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A SCIENTIFIC CORNER

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THE SOLUTIONS, AS SOLVED BY EXPERIENCE, INDICATED!

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Cases like this point up the fact that proper centering is just as important in monocular fitting as in binocular fitting. Too often, badly centered lenses are passed on to the patient with the false justification that since only one eye was being used the centering was of no importance.

"IF IT'S A LENS PROBLEM, LET'S LOOK AT IT TOGETHER"

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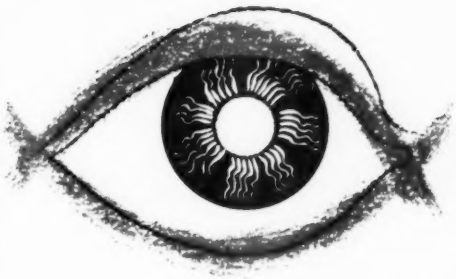

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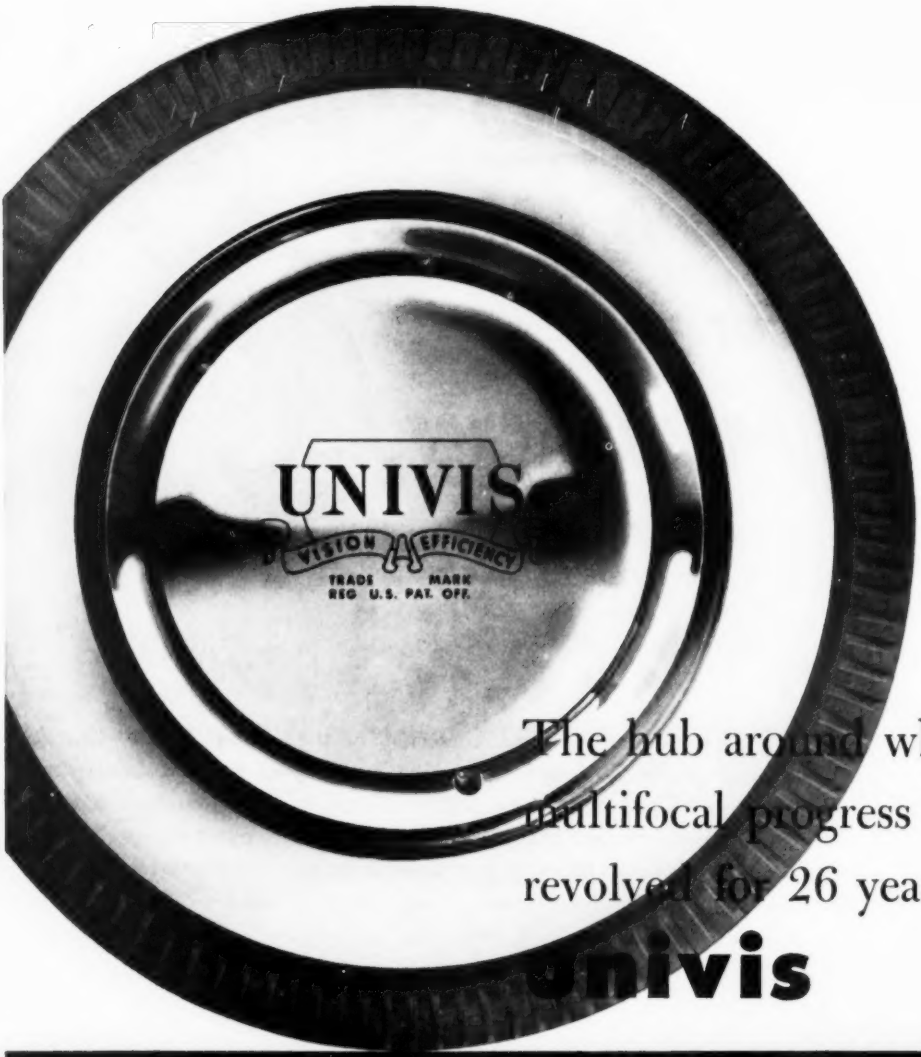

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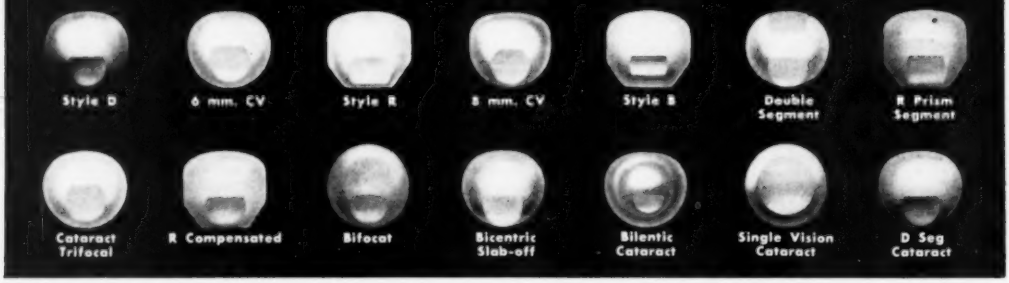

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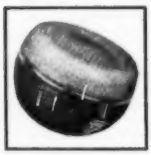

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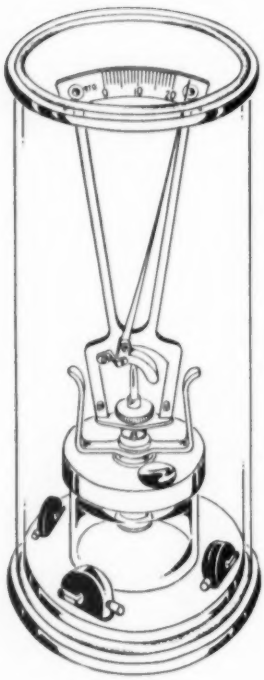

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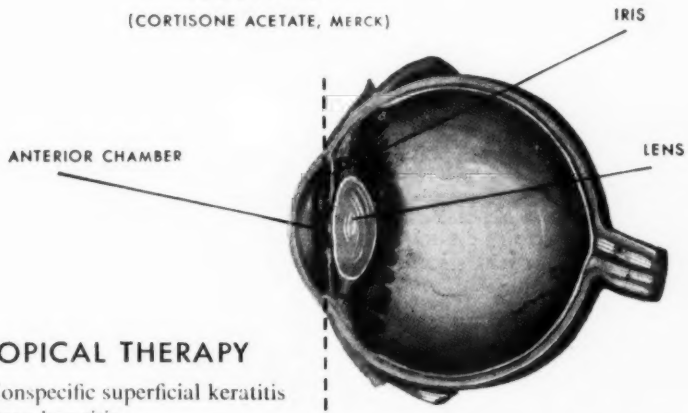

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1. Fine, M., and Goodwin, R. C.: *A.M.A. Arch. Ophth.* **47**:787-797, June 1952.

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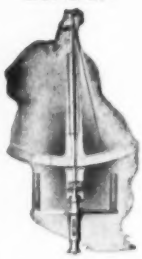

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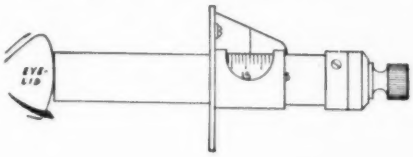

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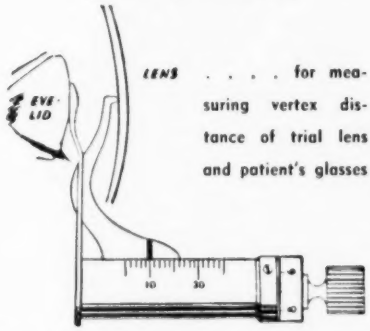

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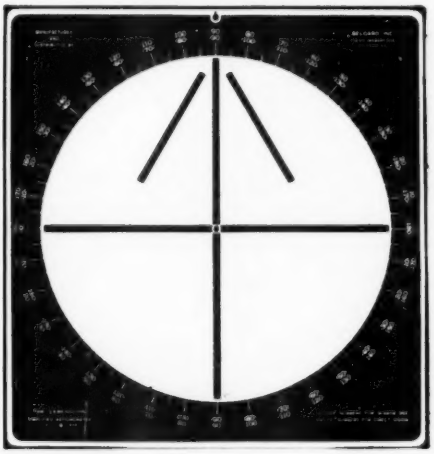

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ALAN C. WOODS
BALTIMORE

A PRELIMINARY report, in 1950, on the diagnostic and therapeutic use of Streptococcus vaccines in nongranulomatous uveitis was presented at the 16th International Congress of Ophthalmology.[1] This report was based on a study of 60 patients with uveitis, 35 of whom had the nongranulomatous and 25 the granulomatous forms. Fourteen of the patients with nongranulomatous uveitis were treated by desensitization with specific bacterial antigens. This preliminary study indicated the value of intracutaneous tests with Streptococcus antigens in the detection of a specific bacterial hypersensitivity, and of intravenous desensitization with the incriminated organisms in the therapy of nongranulomatous uveitis. Since the presentation of this preliminary report, and up to July 15, 1952, similar studies have been made on 148 additional patients with uveitis and specific vaccines prepared for the treatment of 61 of the patients with the nongranulomatous form. It is the purpose of this paper to report the findings and the conclusions drawn from this study of 208 patients (60 in the preliminary report and 148 new patients—107 with granulomatous and 101 with nongranulomatous uveitis).

RECAPITULATION

Under the concept of uveitis as here presented, the granulomatous and the nongranulomatous form are believed to have a different pathogenesis, although in many cases of granulomatous uveitis there may be a superimposed nongranulomatous allergic reaction.

Granulomatous uveitis is believed to be basically due to an actual infection of the tissues with the living organisms which characteristically cause granulomatous disease. In favor of this concept is the clinical picture of insidious onset, long-drawn-out inflammation, exacerbations, and remissions; the organic changes which early occur in the diseased eye, and the histological picture of tissue destruction with an overgrowth of granulomatous tissue, all of which are characteristic of an infectious process. Despite the technical difficulties, actual bacteria can sometimes be demonstrated in the histological sections; and, although there has been little clinical tissue available for culture or animal inoculation, in a few of the cases in which tissue has been available, living organisms could sometimes be demonstrated.

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1. Woods, A. C.: A Clinical Study of Streptococcus Bacterial Sensitivity in Non-Granulomatous Uveitis, Acta XVI Conc. Ophth., London **1**:303, 1950.

In the spontaneous granulomatous uveitis and keratitis which occasionally occur in experimental animals with systemic granulomatous disease (tuberculosis, brucellosis, syphilis) the living organisms in the eye can be demonstrated routinely, either by culture or by animal transmission experiments.

Nongranulomatous uveitis presents a peculiar clinical problem. The anterior uvea is oftener affected than is the posterior uvea. In the anterior form, the disease is characterized by an acute onset, with moderate to violent ciliary congestion, edema of the iris, constriction of the pupil, often fibrin in the anterior chamber, and fine, pinpoint keratic deposits of the lymphoid cell type. In the somewhat rarer posterior form of the disease, the characteristic findings are vitreous haze; fine, dust-like opacities in the vitreous; pronounced retinal and subretinal edema, and sometimes vague, ill-defined exudates. Whether in the anterior or the posterior uvea, the disease is essentially self-limited, the early attacks usually subsiding without any evidence of organic damage to the eye. Recurrences, spaced at intervals of from a few weeks to many months, are the rule rather than the exception. After repeated attacks, organic changes occur in the eye. In the anterior form of the disease, these consist of posterior synechia, atrophy of the iris, capsular clouding of the lens, and often secondary glaucoma. In the posterior form, the vitreous opacities may become heavier and organized, and granular degenerative changes, with disorganization and fine pigmentation, occur in the retina and choroid, sometimes with superficial gliosis. Actual tissue destruction, with heavy glial scarring and massive pigment clumping, rarely if ever occurs. In some cases the surgical eradication of foci of infection brings the attack to an end, and the patient appears cured—a phenomenon which accounts for the early popularity of the doctrine of focal infection. In other patients, unfortunately the great majority, the complete removal of all discoverable foci of infection is without effect; the attacks continue to occur; organic changes gradually develop, and many of the patients go blind. It has recently been found that adequate therapy with the adrenal cortex hormones will control the inflammatory and exudative symptoms of the attacks in some 80% of the patients so treated but will not prevent recurrences. Cultures of the aqueous of patients with nongranulomatous uveitis are uniformly sterile,[2] although the Swiss investigators have reported the presence of what may be dead bacteria in samples of aqueous.[3] Blood cultures are usually sterile, although an occasional case of bacteriemia with streptococci has been reported.[4] Efforts to transmit the disease by animal inoculation have been fruitless. Since the hypothesis that the disease is caused by actual infection of the eye with living bacteria appears untenable, ophthalmologists have been forced to look elsewhere to explain the pathogenesis.

The hypothesis underlying the diagnostic and therapeutic use of bacterial vaccines is as follows:[5] Nongranulomatous uveitis is conceived to be a sterile, allergic reaction dependent on underlying bacterial hypersensitivity. Sensitization of the eye results from prior contact of the ocular tissues with living or dead bacteria

2. Kolmer, J. A.: The Bacteriological and Immunological Aspects of Iritis, with Special Reference to Its Relationship to Bacterial Allergy, Am. J. Ophth. **14**:217, 1931.

3. Amsler, M.: New Clinical Aspects of the Vegetative Eye: Bowman Lecture, Tr. Ophth. Soc. U. Kingdom (1948) **68**:45, 1949.

4. Traut, E. F.: Blood-Culture Studies in Iritis, Am. J. Ophth. **17**:106, 1934.

5. Woods, A. C.: The Influence of Hypersensitivity on Endogenous Uveal Disease (Jackson Memorial Lecture), Am. J. Ophth. **30**:257, 1947.

brought to it by a transient bacteremia, arising from an exogenous source or from an endogenous focus of infection. Such a bacteremia is known to be a relatively common phenomenon. The intoxicating, or reaction-producing, allergin is either soluble bacterial products brought to the eye from a focus of infection or living or dead bacteria from a second bacteriemia with the specific organisms. This hypothesis fits the clinical picture. In addition, there is considerable experimental evidence to support such a view. This experimental work may be summarized as follows:

In 1908 Nicolle and Abt [6] showed that guinea pigs, sensitized by the intraperitoneal injection of horse serum and later given an injection of the same antigen in the anterior chamber, reacted with an acute, self-limited ocular inflammation, which was apparently a nongranulomatous iritis. In 1930 Seegal and Seegal [7] demonstrated that the eye could be specifically sensitized to foreign protein and that anaphylactic reactions could be produced by later contact with the specific antigen. Julianelle [8] showed that when animals were given injections of heat-killed pneumonococci, the tissues of the eye participated in the ensuing hypersensitivity. Almost at the same time, Derick and Swift [9] showed that repeated intracutaneous injections of living nonhemolytic streptococci produced a secondary reaction after the 8th to the 10th day and that simultaneously with the development of this reaction there appeared in the test animals a generalized bacterial type of hypersensitivity. The eye participated in this hypersensitivity, and contact of the ocular tissues with the specific bacterial antigen produced a transient, acute ocular inflammation. In 1932 Brown [10] confirmed and extended these experimental observations and showed that the uveal tract could be sensitized by the injection into the anterior chamber of protein antigens or of killed hemolytic streptococci, and that a sterile nongranulomatous iritis could be evoked by the later intravenous injection of the same antigens. Finally, in 1936, MacLean [11] showed that a classic nongranulomatous iritis could be produced in the untraumatized eye of a rabbit by intracutaneous sensitization with living nonhemolytic streptococci and the later intravenous injection of the same organisms. These various fundamental experimental findings have been abundantly confirmed by many other investigators, to the extent that the anaphylactic and allergic ophthalmic reactions are now recognized procedures in the study of the hypersensitive state.

This idea of an allergic pathogenesis for an inflammatory and degenerative disease process is not new. For many years it had been suggested that rheumatoid

6. Nicolle, M., and Abt, G.: Les anticorps et les albuminoïdes des cellules, Ann. Inst. Pasteur **22**:132, 1908.

7. Seegal, D., and Seegal, B. C.: Local Organ Hypersensitiveness: Experimental Production in Rabbit Eye, Proc. Soc. Exper. Biol. & Med. **27**:390-393, 1930.

8. Julianelle, L. A.: Reactions of Rabbits to Intracutaneous Injections of Pneumococci and Their Products: The Development of Eye Reactivity to Derivatives of Pneumococci, J. Exper. Med. **51**:633, 1930.

9. Derick, C. L., and Swift, H. F.: Reactions of Rabbits to Nonhemolytic Streptococci: General Tuberculin-Like Hypersensitiveness, Allergy, or Hyperergy Following the Secondary Reaction, J. Exper. Med. **49**:615, 1929.

10. Brown, A. L.: Considerations Underlying the Experimental Production of Uveitis, Am. J. Ophth. **15**:19, 1932.

11. MacLean, A. L.: Experimental Iritis: The Ocular Reactions in Rabbits Sensitized to Streptococcus Viridans, Tr. Am. Ophth. Soc. **34**:324, 1936.

arthritis, which is often associated with nongranulomatous uveitis, may be an allergic reaction in the affected joints dependent on a hypersensitivity of the bacterial type.[12]

In the investigation of a specific bacterial hypersensitivity responsible for nongranulomatous uveitis, the streptococci were selected as the starting point, for the following reasons: 1. Exclusive of staphylococci, which cause purulent lesions, the streptococci are the organisms most frequently found in chronic foci of infection. 2. Nongranulomatous uveitis is often associated with rheumatoid arthritis; the streptococci are the organisms usually responsible for the bacterial hypersensitivity found in patients with rheumatoid arthritis, and there is considerable evidence that rheumatoid arthritis is itself an allergic tissue reaction due to a bacterial hypersensitivity.[12] 3. A classic nongranulomatous iritis can constantly be produced by sensitization and intoxication with living or dead Streptococcus antigens.[13] Although the significance of antistreptolysin and antistreptohyaluronidase is something of a controversial matter, nevertheless the recent studies of Schöne and Steen [14] and Dickenson and Leopold [15] on the titer of these substances in the serums of patients with uveitis indicate the probable activity of streptococci in this disease entity.

The streptococci form a complex antigenic group. On the basis of their hemolytic activity, they are divided into the alpha, beta, and gamma groups. Streptococci of the alpha group (viridans form of streptococcus, Schottmüller) form a peculiar zone of green hemolysis around the colonies. The beta streptococci form a clear zone of hemolysis. The gamma group are nonhemolytic.

The alpha streptococci are of low virulence for man. They are commonly found in septic lesions of the mouth and gums and in chronic foci of infection. The antigenic structure is not very clearly understood. It is probable there are no antigenically different polysaccharide fractions in this group. While there are a large number of antigenically distinct strains, the antigenic difference probably depends on differences in the antigenic mosaic of the nucleoprotein fraction.

The beta streptococci are much better understood. On the basis of antigenically different polysaccharide fractions, they are divided into 12 subgroups, A, B, C, D, E, F, G, H, K, L, M, and N. Subgroup A is the most important, containing practically all the virulent pathogens for man. On the basis of an acid-soluble protein, the M substance and a T substance of undetermined nature, some 42 antigenically distinct strains are now recognized in subgroup A. Subgroup B occurs in bovine mastitis and in milk. It contains certainly four main antigenic types and a number of substrains. The most important of the other groups is subgroup F, the minute Streptococcus, which in some cases is responsible for tonsillitis and infection of the

12. Zinsser, H.: Resistance to Infectious Diseases: Exposition of Biological Phenomena Underlying Occurrence of Infection and Recovery of Animal Body from Infectious Disease, with Consideration of Principles Underlying Specific Diagnosis and Therapeutic Measures, Ed. 4, New York, The Macmillan Company, 1931, p. 467.

13. Julianelle,[8] Derick and Swift,[9] Brown,[10] Swift, H.: Rheumatic Fever: Hektoen Lecture, Billings Foundation, J. A. M. A. **92**:2071, 1929.

14. Schöne, R., and Steen, R.: Antistreptolysin Titre and Antistaphylolysin Titre in Iridocyclitis Acuta, Acta ophth. **29**:201, 1951.

15. Dickenson, T. G., and Leopold, I. H.: Antihyaluronidase and Antistreptolysin Titers in Uveitis, to be published.

upper respiratory tract. The other subgroups are apparently of little importance in man; a few pathogens, of low virulence, occur in the C and G groups, while the D, E, H, K, L, M, and N groups are usually nonpathogenic.

The gamma streptococci have not been extensively studied, the probable reason being that they are only occasionally human pathogens. There is some cross fixation between them and some members of Lancefield's subgroup D of the beta streptococci. It is not known whether the different strains have different polysaccharide fractions.

THE CLINICAL PROBLEM

If it is true that nongranulomatous uveitis is an allergic reaction, usually due to a bacterial hypersensitivity to streptococci, one should be able to demonstrate the following factors: 1. A high incidence of specific streptococcic sensitivity in patients with nongranulomatous uveitis. 2. A source whence the sensitizing and reaction-producing allergin might arise. In this connection, one would think first of foci of infection, which often harbor streptococci. Is there a higher incidence of such foci in the nongranulomatous group? 3. A greatly lessened incidence of systemic evidence of granulomatous disease in the nongranulomatous group, ruling out the possibility that the acute nongranulomatous uveitis is a reaction dependent on sensitization and intoxication from organisms which usually cause granulomatous ocular disease. 4. Control of inflammation and prevention of recurrences of nongranulomatous uveitis by proper desensitization of the patient with the specific organisms to which he is sensitive. This is the clinical problem, and these were the four points primarily investigated in this study.

Material for Study.—The 208 patients on whom this study is based were almost without exception patients referred for determination of the etiological factors responsible for recurrent or unexplained uveitis. Excluded were 28 patients in whom, at the time of the first examination, the ocular picture was so confused that it was impossible to tell whether the uveitis was nongranulomatous or granulomatous. Excluded also were a number of patients in whom the hypersensitive state was studied for ocular disease other than uveitis. With these exceptions, the material includes all consecutive patients with uveitis studied from Jan. 1, 1950, to July 15, 1952, together with the 60 patients previously reported on and studied between 1937 and 1949. The great majority of these were ambulant private patients; the others were private or hospital ward patients.

Methods of Study.—At the time of the first examination, the opinion as to the granulomatous or nongranulomatous nature of the uveitis was recorded. The patient was then subjected to a full medical survey, the details of which have been outlined elsewhere.[16] This study included a search for any systemic evidence of granulomatous disease and for foci of infection. If foci of infection were discovered, they were removed surgically, when possible, and the bacterial flora of the focus determined. If any streptococci or other suspicious organisms were found, special test vaccines were prepared from these and were added to the diagnostic set for that patient. The patient was finally tested out against the full stock diagnostic set of Streptococcus vaccines, separate, individual tests being made with each strain. About one-half the patients were also tested with a Gonococcus antigen. In the later stages of the investigation histoplasmin and toxoplasmin antigens were added. At the conclusion of the study of each patient, the amassed results were analyzed, and, when possible, a probable or presumptive etiological diagnosis was made. The criteria for such diagnosis have already been outlined.[16]

The Diagnostic Vaccine Set.—The original diagnostic set consisted of four strains of the alpha streptococci, all 42 strains of the subgroup A of the beta streptococci (Lancefield classification), 15 strains of subgroup B, a number of representatives of the C, D, F, and G subgroups,

16. Woods, A. C.: Endogenous Uveitis, Manual of Am. Acad. of Ophth. & Otol. 1949.

and one representative of the gamma streptococci. As the study progressed, the importance of the alpha group became evident, and as new strains of antigenically distinct alpha streptococci were isolated from foci of infection, they were added to the diagnostic set. Since few reactions were noted to the subgroup B strains, all but six of these strains were eliminated. No reactions to the D, E, or G subgroup were observed, and these strains were omitted. One strain of the C and F groups and the gamma Streptococcus were retained. The present set consists of 10 antigenically distinct strains of alpha streptococci, 42 strains of subgroup A of the beta streptococci, six strains of subgroup B, one representative of the C and F strains, a gamma Streptococcus, a Gonococcus, histoplasmin, and toxoplasmin.

The test dose was 0.1 cc. of 1 : 10 dilution of T_{∞} (electrophotospectrometer) concentration of each strain. By a trial-and-error procedure, it was found this dose gave good reactions in patients with rheumatoid arthritis and gave no, or insignificant, reactions in a large control group of cataract patients without uveitis or any demonstrable foci of infection. The sites of the test injections were inspected at the end of 15 minutes and read at 48 hours. Results were recorded on a zero (—) to + + + + scale. A + reaction indicated erythema of 5 to 7 mm. with only slight induration; a + + reaction, erythema of 8 to 15 mm. with induration; a + + + reaction, erythema of 15 to 25 mm. with marked induration but without necrosis, and a + + + + reaction, an equally large reaction with evidence of necrosis. The positive reactions as here reported were all + + or greater, weaker or doubtful reactions being regarded as negative for the purposes of this study. The positive reactions were all of the delayed type, coming on 24 to 48 hours after the test injection. Immediate reactions were only occasionally found and, when observed, appeared to have little correlation with the final reading.

RESULTS

I. *Incidence and Nature of the Specific Hypersensitivity.*—The patients are reported on in two groups on the basis of the original probable ocular diagnosis—nongranulomatous and granulomatous uveitis. There were 101 patients in the nongranulomatous group and 107 patients in the granulomatous group.

In the nongranulomatous group an undue bacterial hypersensitivity was present in 90 patients, or 89%. Eighty-eight of these patients showed a hypersensitivity to one or more strains of Streptococcus vaccines. One patient reacted to a stock Gonococcus vaccine, and one, to a Pseudomonas aeruginosa (Bacillus pyocyaneus) isolated from his tonsil, neither of these showing any reaction to the stock Streptococcus vaccines. The 88 reactions to Streptococcus vaccines were divided as follows: Seven patients reacted only to autogenous streptococci, i. e., organisms cultivated from their own foci of infection; 73 patients reacted to one or more strains of the stock vaccines, and 8 patients reacted to streptococci cultivated from their own foci of infection and also to various of the stock strains. Two of the reactors to stock Streptococcus vaccines also showed incidental reactions to other organisms —one to a stock Gonococcus vaccine and one to a vaccine of Ps. aeruginosa cultivated from his own focus of infection. Eleven of the patients with nongranulomatous uveitis gave negative responses, failing to show any definite reaction to any of the stock vaccines or, when so tested, to any organisms cultivated from their foci of infection. These figures for the nongranulomatous group, 89% with positive reactions and 11% with negative reactions, are in contrast with the 20%, or 21 patients, with positive reactions, and 80%, or 86 patients, with negative reactions among the 107 patients with granulomatous uveitis. These results are shown in Table 1.

A more detailed analysis of the positive reactions to Streptococcus vaccines gives the following results:

Nongranulomatous Group: A. Over-all picture. Seven patients reacted only to autogenous vaccines prepared from streptococci cultured from their own foci of infection. Four of these organisms were alpha streptococci; two were beta streptococci, and one was a gamma form. Sixty patients reacted only to straight stock vaccines—1 to an alpha strain and 59 to one or more strains of the subgroup A of the beta streptococci. Eighteen patients showed cross reactions among the alpha, beta, and gamma Streptococcus vaccines—10, among stock vaccines of the various groups and 8 between autogenous and stock strains. Three patients showed cross reactions among the subgroups of the beta Streptococcus vaccines—one between subgroups A and B, and two between subgroups A and F. This analysis is presented in Table 2.

TABLE 1.—*Incidence of Bacterial Hypersensitivity in Patients with Nongranulomatous and Granulomatous Uveitis*

Type of Uveitis	No. of Patients	Specific Bacterial Hypersensitivity				Total Positive Reactions	Total Negative Reactions
		Stock Streptococcus Vaccines	Stock and Autogenous Streptococcus Vaccines	Autogenous Streptococcus Vaccines Only	Other Organisms		
Nongranulomatous	101	73	8	7	2	90, or 89%	11, or 11%
Granulomatous	107	21	0	0	0	21, or 20%	86, or 80%

TABLE 2.—*Distribution of Eighty-Eight Positive Reactions to Streptococcus Vaccines Occurring in One Hundred One Patients with Nongranulomatous Uveitis*

Type of Streptococcus	Straight Reactions		Cross Reactions	
	To Single Strains or Subgroups Only			
	Autogenous Vaccine	Stock Vaccine	To Other Groups	To Other Subgroups
Alpha	4	1	17	..
Beta	2	59	18	3
Gamma	1	0	3	..
Totals	7	60	18*	3

* All patients giving cross reactions to alpha or gamma vaccines likewise gave cross reactions to beta vaccines and are included in the 18 giving cross reactions to beta streptococci.

B. Intergroup cross reactions. Of the 18 intergroup cross reactions, there were 5 between autogenous alpha vaccines and beta A vaccines; 1 among an autogenous alpha vaccine, a beta A vaccine, and a stock gamma vaccine; 8 between stock alpha vaccines and beta A vaccines; 2 among stock alpha, beta A, and beta B or F vaccines; 1 between a stock alpha vaccine, a beta B and F vaccine, and an autogenous gamma vaccine, and 1 between beta A vaccines and an autogenous gamma vaccine. This analysis is shown in Table 3.

C. Alpha reactors. Four patients reacted to autogenous alpha vaccines only, and one to a stock alpha vaccine only. Seventeen patients showed cross reactions among alpha and beta, or alpha, beta, and gamma vaccines. Six of these reactions were between autogenous alpha and other group vaccines, and 11 between stock

alpha and beta or gamma vaccines. There were, thus, 22 alpha reactors in all—10 to autogenous organisms and 12 to stock vaccines.

D. Beta reactors. Two patients reacted to autogenous beta vaccines only. In neither instance was the subgroup determined. Since the patients did not react to any of the stock beta vaccines, both obviously had hemolytic strains, not represented in the present diagnostic set.

Fifty-nine patients reacted only to various of the subgroup A vaccines. Three patients showed cross reactions between subgroup A strains and subgroup B or F strains. Seventeen of the 18 patients who gave cross reactions to the alpha or gamma vaccines reacted to strains of the subgroup A, making 79 patients in all who reacted to beta A vaccines. The notable observation in these patients was the tendency to multiple reactions to the various 42 component strains. This, indeed, was the rule rather than the exception. Thus, of the 79 reactors to beta A vaccines,

TABLE 3.—*Breakdown of Eighteen Intergroup Cross Reactions*

No. of Cross Reactions	Alpha; Beta A Only		Stock Alpha; Beta A; Beta B or F	Autogenous Alpha; Beta A; Stock Gamma	Stock Alpha; Beta B-F; Autogenous Gamma	Beta A; Autogenous Gamma
	Autogenous Alpha	Stock Alpha				
18	5	8	2	1	1	1

TABLE 4.—*Distribution of Reactions to Vaccines of the Subgroup A of the Beta Streptococci*

Type of Uveitis	Beta Streptococci, Subgroup A			
	Total No. of Reactors	Reactors to 1-2 Strains	Reactors to 3-9 Strains	Reactors to 10 + Strains
Nongranulomatous	79	13	59	7
Granulomatous	21	7	11	3
Totals	100	20	70	10

only 13 reacted to 1 or 2 strains, while 59 reacted to from 3 to 9 strains, and 7 to 10 or more strains, 2 of these reacting strongly to all 42 strains. This analysis is shown in Table 4.

There were only three reactors to the subgroup B vaccines and six reactors to the subgroup F vaccine. These patients also reacted to various other stock or autogenous vaccines. Although few reactions were observed to these subgroups, all the reactions were rather intense, and hypersensitivity to those strains, while infrequent, may be of importance.

E. Gamma reactors. Only four patients reacted to the gamma vaccines. One of these showed a violent 4 + reaction to an autogenous vaccine from his own focus of infection and did not react to any of the stock strains. Two others showed reactions to autogenous gamma vaccines and also to stock alpha and beta vaccines. The last patient reacted both to stock gamma vaccines and to an autogenous alpha vaccine, as well as to various beta A strains.

F. Autogenous vaccines. Material from foci of infection was cultured for 31 of the patients in the nongranulomatous group and the bacterial flora determined in 30 of these, one culture showing no growth. The majority of these cultures yielded a mixed flora—streptococci together with staphylococci, Escherichia coli,

Micrococcus catarrhalis, and other contaminants. In 26 cultures, however, streptococci were present, occasionally in pure culture. Two cultures yielded Ps. aeruginosa, one in pure culture and one in combination with a Staphylococcus. The remaining two cultures yielded Esch. coli and a Staphylococcus, respectively, in pure cultures.

In the early stages of the study, individual vaccines were made from each organism found in the various cultures. It was soon apparent that the obvious contaminants, such as Esch. coli, M. catarrhalis, and staphylococci, did not give positive reactions in the tests with their vaccines, and thereafter these organisms were disregarded except in the two instances in which they were present in pure culture. Every Streptococcus, however, was plated out in pure culture, its type determined, and a test vaccine prepared. Vaccines were likewise prepared from the two Ps. aeruginosa organisms. When the individual patients were tested with these vaccines, the following results were obtained: Ten patients reacted to their own alpha

TABLE 5.—*Reactions of Thirty Patients with Nongranulomatous Uveitis Tested Against Organisms Isolated from Their Focus of Infection*

Alpha Streptococci			Beta Streptococci			Gamma Streptococci			Other Organisms (Pure Cultures)									Totals		
									Staphylococcus		Esch. Coli		Ps. Aeruginosa							
+	−	Cross Reactions	+	−	Cross Reactions	+	−	Cross Reactions	+	−	+	−	+	−	Cross Reactions			+	−	Cross Reactions
10	10	6	2	1	0	3	0	2	0	1	0	1	2	0	1			17	13	9

organisms, and 4 of these showed no reaction to any of the stock Streptococcus vaccines. Two patients reacted to their own beta streptococci and did not react to other streptococci. All three patients in whom gamma streptococci were isolated were hypersensitive to their own organisms, one being insensitive to other streptococci, while the other two also reacted to stock Streptococcus vaccines. The two patients in whom Ps. aeruginosa was found in their foci of infection were both hypersensitive to these organisms, one failing to react to any of the Streptococcus vaccines and the other reacting to various alpha and beta stock vaccines. The patients in whom Esch. coli and staphylococci only were found did not react to test vaccines of these organisms. These results are shown in Table 5.

Granulomatous Group: The positive reactions of the 21 patients in the granulomatous group were all confined to various strains of the subgroup A of the beta streptococci. No reactions were observed to any of the alpha vaccines, to the beta B or F vaccines, or to the gamma vaccine. The reacting patients in the granulomatous group showed the same tendency to multiple reactions to the various component strains of the beta A vaccines as did the reacting patients in the nongranulomatous group. This distribution is shown in Table 4.

II. *Foci of Infection.*—Foci of infection, whether in the teeth, paranasal sinuses, tonsils, nasopharynx, or genitourinary tract, were present in 56 patients, or 55%, of the nongranulomatous group. Again, this contrasts with an incidence of similar foci in 31 patients, or in 28%, of the granulomatous group. The latter figure, 28%,

is almost exactly the incidence (29%) of such foci found in 503 cataract patients without any evidence of uveitis.[17] These figures are shown in Table 6.

An analysis of the incidence of foci of infection in patients of both groups showing a specific hypersensitivity to streptococci is of interest. In the nongranulomatous group the incidence of foci of infection in the hypersensitive patients (53.4%) was almost exactly that of the entire group (55.0%). On the other hand, in the granulomatous group, 13 (65%) of the 20 hypersensitive patients had foci of infection, in contrast to an incidence of 29.5% for the entire group and of 9.7% for the insensitive patients of this group. This suggests that the bacterial hypersensitivity shown by the small number of patients in the granulomatous group may possibly be related to an incidental focus of infection. This analysis is presented in Table 7.

TABLE 6.—*Incidence of Foci of Infection in Patients with Nongranulomatous and Granulomatous Uveitis*

Type of Uveitis	No. of Patients	Total Incidence of Foci of Infection	
		Positive	Negative
Nongranulomatous	101	56, or 55%	46, or 45%
Granulomatous	107	31, or 28%	76, or 72%

TABLE 7.—*Incidence of Foci of Infection in Hypersensitive Patients*

Type of Uveitis	No. of Patients Showing Undue Bacterial Hypersensitivity	No. and Percentage of Hypersensitive Patients Showing Foci of Infection	No. and Percentage of Foci of Infection	
			Entire Group	Insensitive Patients
Nongranulomatous (102 patients)	89	48, or 54%	56, or 55%	8, or 73%
Granulomatous (107 patients)	20	13, or 65%	31, or 29.5%	7, or 9.7%

III. *Incidence of Granulomatous Disease.*—Evidence of granulomatous disease was found in only 10, or 10%, of the patients with nongranulomatous uveitis. In 9 of these 10 patients there were evidences of an old tuberculous infection, manifested by undue hypersensitivity to tuberculin and roentgenographic changes in the chest. This incidence is probably somewhere near the frequency of such evidence of tuberculous infection in normal persons. In one patient there was evidence of a former Brucella infection. In contrast, systemic evidences of granulomatous disease were found in 83 (78.5%) of the patients with granulomatous uveitis. Among the various granulomatous diseases of which evidences were found were tuberculosis, brucellosis, syphilis, sarcoidosis, Vogt-Koyanagi disease, and virus infections. In two patients toxoplasmosis was suspected, and in two the findings were compatible with a diagnosis of nonfatal histoplasmosis. This analysis is shown in Table 8.

17. Guyton, J. S., and Woods, A. C.: Etiology of Uveitis: Clinical Study of 562 Cases, Arch. Ophth. **26**:982, 1941.

IV. *Effect of Desensitization.*—Desensitization of the patient with antigens composed of the specific bacteria to which he is sensitive is a fundamental therapeutic attack on the pathogenesis of nongranulomatous uveitis as here predicated. The other recognized forms of therapy are only symptomatic. The use of antihistaminics, which supposedly compete with histamine for a place on the target cells, has been quite unsuccessful in nongranulomatous uveitis. While the adrenal cortex hormones suppress inflammation and protect the fixed cells, they do not attack the cause of the disease or prevent recurrence. The isolation of the patient from the specific allergins, widely disseminated and prevalent organisms, is, unfortunately, impossible in most cases.

Desensitization consists of the administration of the antigen to the hypersensitive patient in doses sufficiently small not to cause a clinical reaction. By the repeated administration of such subclinical doses, the antigen gradually enters in combination with the antibody on the cell until the combining power of the antibody has been satisfied. When this status has been attained, larger doses of the antigen do not cause a reaction—a refractory or desensitized state has been reached. The

TABLE 8.—*Evidences of Granulomatous Disease in Patients with Granulomatous and Nongranulomatous Uveitis*

Type of Uveitis	Evidence of Systemic Granulomatous Disease					Total Incidence	
	Tuberculosis	Brucellosis	Sarcoidosis	Syphilis	Others	Positive	Negative
Granulomatous uveitis (107 patients)	50	14	6	5	8	83 (78.5%)	24 (22.5%)
Nongranulomatous uveitis (102 patients)	9	1	0	0	0	10 (9.8%)	92 (90.2%)

fundamental points to be observed in desensitization are that the antigen be administered to the patients in quantities below the threshold of a clinical reaction, that the dose of antigen be increased as the point of reactivity recedes, and that once a desensitized status has been attained, the injections be continued on a maintenance dosage to prevent the recurrences of hypersensitivity, which, unfortunately, are frequent.

Local ocular reactions—acute, short attacks of classic nongranulomatous iritis—were noted in three treated patients. One of these patients received the vaccine subcutaneously and two intravenously. While these reactions supported the concept of the relationship of the administered Streptococcus to the ocular inflammation, they were distressing both to the patient and to the physician. In one patient, treated subcutaneously, reactions occurred after injection of each decreased dose until the low concentration of 1:10,000 was reached. Thereafter, desensitization proceeded uneventfully. In another patient, repeated ocular reactions, even to greatly decreased doses, made it necessary to abandon the desensitization therapy.

Techniques of Desensitization: A. Preparation of the vaccine. Fundamental to the preparation of any vaccine is a thorough knowledge of the antigenic mosaic of the organisms involved. With streptococci, the vaccine should be prepared from "smooth" colonies, which contain both the specific carbohydrate and the nucleoprotein fractions. Each individual strain is prepared from a 24-hour-broth culture; the organisms are repeatedly washed in 0.85% saline, containing 0.5% phenol for removal of all traces of broth and exotoxin; they are then taken up in saline with 0.5% phenol, and the turbidity of the suspension is adjusted to a T_{∞} dilution on the spec-

trophotometer. The various strains to which the patient was hypersensitive are then pooled to make the desired final vaccine. This vaccine is then heated for one hour at 60 C. and tested for sterility. Finally, 1:10 and 1:100 dilutions of this are prepared with saline containing 0.5% phenol.

B. Dosage. The usual schedule of dosage follows: The initial intravenous injection is 0.1 cc. of the 1:100 dilution of the final T_{∞} dilution. The patient should be carefully watched for fever, leucocytosis, or evidences of a systemic reaction. If no reaction is observed, the next dose is given at a three or four day interval, the amount given being increased 0.1 cc. at each injection until a dose of 0.9 cc. of the 1:100 dilution is taken without reaction. The 1:10 dilution is then used, the initial dose being 0.1 cc. If this is taken without reaction, the dose is then increased 0.1 cc. at each injection until 0.9 cc. of the 1:10 dilution is taken. The straight T_{∞} dilution is then used, 0.1 cc. being the first dose, this dose is similarly increased until a dose of 0.5 cc. is taken, which is considered the maximum maintenance dose and is repeated at 4-day intervals for a period of about two months. The patient should then be tested to see whether the cutaneous reactivity has been abolished. If not, the dose is continued at four-day intervals for a further period, of several months. When the cutaneous reactivity is no longer present, the interval between injections is lengthened to one week, and the use of the vaccine is continued for several months. If reactions are observed at any level, the dose is immediately dropped to one-tenth that causing the reaction, and is then gradually increased if no further reaction is observed.

C. Method of Administration. Desensitization with bacterial antigens introduces the problem of the method of administration. It has been clearly shown that the repeated intracutaneous injection of streptococci in experimental animals incites a high degree of cutaneous hypersensitivity or reactivity, with low serum precipitin and agglutinin titers.[9] On the other hand, the intravenous injection of the bacterial antigens in normal animals either does not produce the characteristic skin reaction or produces only a low degree of cutaneous reactivity and incites high precipitin and agglutinin titers.[18] Therefore, if a bacterial suspension is to be used with the primary idea of desensitizing an already hypersensitive animal, it would appear preferable to administer the vaccine intravenously, by which route there are little danger of increasing sensitivity and good prospects of desensitizing, and possibly immunizing, the patient. This was the idea underlying Wainwright's intravenous use of Streptococcus vaccines in the treatment of rheumatoid arthritis.[19] It was the method selected for attempted desensitization of patients with nongranulomatous uveitis.

Results: Vaccines were prepared for 61 of the hypersensitive patients with granulomatous uveitis. These patients were then referred back to their own physicians for treatment. While a number returned for post-treatment examination and redetermination of their ocular condition and hypersensitivity status, the greater number did not, feeling that they were cured and that there was no necessity for returning to Baltimore for further observation. For many patients, therefore, the results here noted are based on the reports of their referring physicians.

These 61 treated patients fall into the following groups: Eight patients have been lost and efforts to trace them or to obtain information about them have been fruitless. Two patients early abandoned vaccine treatment when they discovered their attacks could be satisfactorily controlled by topical cortisone therapy. Fifteen patients are still under treatment, or the period of observation after completion of treatment is too short to permit evaluation of the end-result. At last reports, all were progressing satisfactorily, although for two the information obtained was too meager to permit any conclusions. The remaining 36 have all been under observa-

18. Derick and Swift[9]; McEwen, C., and Swift, H. F.: Cutaneous Reactivity of Immune and Hypersensitive Rabbits to Intradermal Injections of Homologous Indifferent Streptococcus and Its Fractions, J. Exper. Med. **62**:573, 1935.

19. Wainwright, C. W.: Treatment of Chronic Rheumatoid Arthritis with Streptococcus Vaccine on the Basis of Skin Sensitivity, J. A. M. A. **103**:1357, 1934.

tion sufficiently long to permit evaluation of the results of therapy. Thirty-four of these patients were treated intravenously and two subcutaneously. The results in these patients are shown in Table 9. For 27 of these patients the treatment is recorded as successful. In 25 of these patients the uveitis subsided completely, and there have been no recurrences; in 2 there were recurrences several months after discontinuation of treatment. These patients were retested, and it was found that the sensitivity had returned synchronously with the relapse in the ocular condition. After further treatment there was a subsidence of all activity; and after desensitization was again accomplished there have been no further relapses. After the completion of treatment, 11 of the patients treated successfully were retested with the vaccines to which they were formerly sensitive and gave completely negative results. Desensitization had been accomplished. Three patients are classified as showing "improvement." These patients have been under prolonged treatment and are still moderately sensitive to the incriminated streptococci. However, the attacks now occur only at greatly prolonged intervals and are mild in intensity, fading in a few days. Desensitization in these patients has been a long and difficult process, punctu-

TABLE 9.—*Results of Specific Desensitization in Thirty-Six Patients with Nongranulomatous Uveitis*

Results	No. of Patients	Period of Observation	Recurrences	Comment
Success	11	3-12 yr.	2	Recurrences after termination of treatment, synchronous with return of sensitivity; none after further treatment
	16	6 mo. to 3 yr.	None	
Condition improved	3	6 mo. to 3 yr.	Several	Mild recurrences at greatly prolonged intervals
Failure	6	6 mo.	Many	One "failure"; treatment discontinued on account of repeated focal and systemic reactions

ated with reactions which have made it necessary to lower and adjust the dosage. For six patients the treatment was recorded as "failure." In five of these patients the intravenous administration of the vaccine over an adequate period had no effect on the severity or the frequency of the attacks. It is probable that the hypersensitivity detected in these patients was not etiologically related to the uveitis and desensitization was therefore without value. In the last patient treatment was early abandoned on account of focal ocular reaction, which followed 24 to 48 hours after each injection (Table 9).

COMMENT

This study has revealed four significant points, which may be listed and commented upon as follows:

1. A high proportion (89%) of patients with nongranulomatous uveitis showed a specific bacterial hypersensitivity. This contrasts with an incidence of 20% of similar sensitivity in patients with granulomatous uveitis. With four exceptions (one patient was sensitive to a Gonococcus only; one to an autogenous Ps. aeruginosa only, and two, to streptococci and also, respectively, to a stock Gonococcus and to an autogenous Ps. aeruginosa), this bacterial sensitivity was entirely to various strains of streptococci. The streptococci, however, were the only organisms routinely investigated, although gonococci were tested for in about one-half the patients, and a number of individual tests were done with miscellaneous organisms

isolated from a focus of infection in the particular patients. Even with the streptococci the investigation has been incomplete. Undoubtedly, many pertinent strains, especially of the alpha group, have been omitted. Despite this deficiency in the diagnostic set, a remarkably high incidence of a specific Streptococcus sensitivity was found. This high incidence, especially in conjunction with the other findings, strongly suggests a relationship between the specific hypersensitive state and the cause of the nongranulomatous uveitis.

The nature of the streptococcic sensitivity is of considerable interest. As pointed out in Tables 3 and 4, multiple reactions to various strains were the rule rather than the exception. These multiple reactions bring up the question of the immunological entity of the various groups and strains within the subgroups.

There were 22 patients in all who reacted to alpha vaccines, and 17 of these showed cross reactions to various Streptococcus vaccines of other groups, chiefly to the subgroup A of the beta streptococci. This would, at first glance, suggest that many of the alpha streptococci either do not produce specific sensitizing antibodies or have a common antigenic factor with some of the beta group. Against this view are the facts (*a*) that in this series there were five patients who reacted to alpha streptococci only (one to stock and four to autogenous strains) and who showed no reactions to any of the other diagnostic Streptococcus vaccines, and (*b*) that the great majority of the reactors to beta vaccines did not react to any of the alpha antigens. It would, therefore, seem more probable that the cross reactions shown to beta vaccines by alpha reactors are the result of a prior mixed infection with the two groups.

There were 82 patients in the nongranulomatous group and 21 patients in the granulomatous group who reacted to some beta Streptococcus vaccine. Of these 103 beta Streptococcus reactors, 100 reacted to subgroup A vaccines, and 80 reacted to this subgroup only. This high incidence of hypersensitivity to a single subgroup indicates the overwhelming importance of subgroup A, which is known to contain the great majority of the virulent pathogens for man. Further, the frequent reaction of an individual patient to a number of strains within this subgroup strongly suggests that within it there may be some fairly common antigenic constituent, resulting in a tendency to the formation of group-specific antibodies.

There is insufficient information in this study to permit one to make any surmise concerning the possible specificity of the gamma group organisms. However, in this series, there was one patient, violently sensitive to a gamma organism isolated from his own focus of infection, who showed no reaction to any of the other diagnostic Streptococcus vaccines and who achieved a notable therapeutic result on desensitization with the specific organism.

In the light of these findings, it would seem probable that a positive intracutaneous reaction to different strains of streptococci is an indication of a true immunological reaction to a former infection with these strains, an anamnestic response manifested by the formation of specific sensitizing antibodies, although with the subgroup A organisms there is a tendency to the formation of group-sensitizing antibodies. This is in line with the conclusion of Dawson and Olmstead,[20] who

20. Dawson, M. H., and Olmstead, M.: Agglutination and Precipitation Reactions in Rheumatoid Arthritis with Hemolytic Streptococci Groups A to G, Proc. Soc. Exper. Biol. & Med. **34**:80, 1936.

studied the agglutinin and precipitin reactions to streptococci in patients with rheumatoid arthritis and pointed out the characteristic specific reactions and overwhelming importance of the subgroup A organisms. Similarly, Wainwright [21] studied the multiple agglutinins to hemolytic streptococci in similar patients. Using the absorption technique, he regularly found complete dissociation of the agglutinins of the various groups, but absorption with one strain removed all agglutinins to other strains of the same group, indicating a group, rather than a strain, specificity. These studies suggest that it is possible that the sensitizing antibody response is more specific than the agglutinin or precipitin response, and that with the subgroup A organisms there is a strong tendency to a group, rather than a specific strain, response.

2. Foci of infection, potential reservoirs from which a bacterial hypersensitivity might arise, are much more frequent (55%) in patients with nongranulomatous uveitis than in patients with granulomatous uveitis (28%). This finding is suggestive, but far from conclusive, evidence that such foci of infection may be related to the specific bacterial sensitivity and furnish the source for the intoxicating allergin. Thus, of 30 patients with active foci of infection in whom the bacterial flora of the foci was determined, 17 showed strong reactions to organisms cultivated from these foci, and 8 of these (Table 4) showed no reaction to any of the stock strains of streptococci. In these eight patients it is probable the organisms in the foci of infection were directly responsible for the specific hypersensitivity. The nine other patients who reacted to autogenous organisms also showed reactions to some of the stock Streptococcus strains; there is, therefore, no direct reason to incriminate the organisms recovered from the foci of infection. Moreover, when one determines the bacterial flora of a focus of infection, there is no assurance that the organisms cultivated are the ones primarily responsible for the original infection. They may be only secondary invaders.

The material presented in Table 7 is also suggestive rather than conclusive. There was no statistical difference between the incidence of foci of infection in the hypersensitive and that in the insensitive patients of the nongranulomatous group. The high incidence of foci of infection (65%) in the hypersensitive patients of the granulomatous group as compared with the low incidence (9.7%) in the insensitive patients suggests that such foci might be concerned in the cutaneous reactivity to bacterial antigens; but the number of cases is so small that the difference is without statistical significance. Moreover, those patients were not tested to organisms recovered from their foci. All that can be said is that the presence of active foci of infection in hypersensitive patients gives a possible explanation for the hypersensitivity. The one piece of solid evidence here adduced that bolsters this assumption is the demonstration that in eight patients the organisms cultivated from the foci of infection were the only ones to which these patients showed a hypersensitivity.

3. The incidence of systemic evidence of granulomatous disease in patients with nongranulomatous uveitis (9.8%) is less than that in patients with granulomatous uveitis (78.5%). This difference would be expected, but it is solid evidence against the assumption that attacks of nongranulomatous uveitis are the result of a hyper-

21. Wainwright, C. W.: The Presence of Multiple Agglutinins in the Serum of Patients with Chronic Rheumatoid Arthritis, Bull. Johns Hopkins Hosp. **61**:358, 1937.

sensitivity to organisms that cause latent granulomatous disease. In other words, nongranulomatous uveitis is a clinical entity in its own right, and is in no way related to granulomatous disease.

4. Desensitization of the hypersensitive patient with nongranulomatous uveitis was successful in 27 of 36 such patients who were adequately treated and observed. Three patients showed improvement, and for six the treatment failed. In the evaluation of any desensitization procedure, allowances must be made for the difference in reactions in different patients. Thus, many patients take the vaccine without reaction, reach the maximum maintenance dose in approximately six months, appear completely desensitized, and stop treatment without recurrences or sequelae. Other patients have difficulty, and show systemic, and occasionally focal, reactions of varying degree, making it necessary to lower and adjust the dose. Thus, a much longer time is required to achieve even partial desensitization. Occasionally it may be impossible to desensitize the patient.

In this study, the criteria for recording the desensitization of a patient as a "success" were as follows: (*a*) The patient should have taken the vaccine for at least six months; if treatment was then discontinued, there should follow a minimum period of at least six months in which there was no evidence of a return of the uveitis. The actual average periods of post-treatment observation in the cases in which desensitization was reported as a "success" were as follows: 10 months, for 12 patients; 1 to 2 years, for 10 patients, and 8 years, for 5 patients. (*b*) If there was a recurrence after treatment had been stopped, a return in sensitivity to the specific organisms should also have occurred, and further treatment should again desensitize the patient and prevent further recurrences. (*c*) If desensitization had not been completed in the usual time and therapy was still in process, there should be a period of at least one year without activity or recurrences of any kind while the patient is under treatment. In other words, desensitization was considered successful only if adequate treatment, whether in one course, intermittent, or continuous, had controlled the uveitis and prevented recurrences over what appeared to be an adequate period of observation. Actually, 18 patients achieved complete desensitization after one course of treatment, had no, or only, minor reactions, and had no recurrences. Nine patients are still under continuous or intermittent treatment to maintain desensitization and have been free from symptoms over the prescribed period.

This evidence strongly indicates a cause-and-effect relation between the vaccine treatment and the therapeutic result. That a remission of inflammation and absence of recurrences went hand-in-hand with desensitization does not prove that desensitization *per se* was the mechanism responsible for the therapeutic effect. It is possible, although unlikely, that the beneficial result may be due to some other immunological process. The specific agglutinins and precipitins were not followed in these patients. One would expect them to have been stimulated by the vaccine treatment, and an increased agglutinin and precipitin titer might well protect against intoxication. However, since all the patients had repeated attacks when in the hypersensitive state, and in the great majority all attacks ceased when this hypersensitivity was neutralized, it is logical to conclude that the specific bacterial hypersensitivity was etiologically related to the nongranulomatous uveitis.

The cumulative evidence that patients with nongranulomatous uveitis have a higher incidence of a specific bacterial hypersensitivity, an increased incidence of foci of infection, and a low incidence of systemic evidence of granulomatous disease, and that they obtain a therapeutic effect by specific desensitization, all confirm the original hypothesis that nongranulomatous uveitis is a bacterial allergic reaction. It further indicates the importance of the streptococci in such a hypersensitive reaction. The most important group of streptococci is undoubtedly the subgroup A of the beta group, and the next, the alpha group. Subgroup F of the beta group and the gamma group may also produce a specific hypersensitivity, but much less frequently than the other groups. It is quite possible that gonococci and miscellaneous pathogens may also occasionally be the responsible organisms.

There is nothing in these studies to explain the mechanism of intoxication other than the suggestive evidence already outlined that in some cases the intoxicating allergin may arise from a focus of infection. A great number of patients dated the recurrences of their ocular inflammation to an immediately preceding infection of the upper respiratory tract, and it is quite probable that in many instances a second infection with widely prevalent organisms was the source which supplied the intoxicating allergin.

The detection and treatment of a specific bacterial allergy is a time-consuming procedure, wearisome both to the physician and to the patient. It requires the full cooperation of a well-equipped bacteriological laboratory to maintain a proper diagnostic set, to prepare the specific vaccines, and to determine the flora of a focus of infection. Even when a bacterial hypersensitivity has been demonstrated, it is difficult to say whether it is specifically responsible for the ocular inflammation. The only way in which such relationship can be proved is either the production of ocular focal reactions after the administration of the vaccine (a procedure which should be avoided if possible) or the long, trial-and-error procedure of desensitization. Failure to produce a therapeutic result by desensitization once a bacterial hypersensitivity has been established is probably an indication that the hypersensitivity detected was not the one etiologically related to the ocular disease, rather than an invalidation of the basic hypothesis. It is surprising that the ratio of therapeutic success was so high, and this indicates the overwhelming importance of the streptococci, a group of organisms in which the diagnostic set, while still incomplete, is at least fairly comprehensive. It is to be hoped that future investigations may result in the development of a method of simplifying the diagnostic routine and lead to the production of a polyvalent vaccine which will be efficacious. At present there appears to be no bright prospect of these eventualities.

SUMMARY AND CONCLUSION

Patients with nongranulomatous uveitis showed an amazingly high incidence of bacterial hypersensitivity (89%) as compared with patients with granulomatous uveitis (20%).

With occasional exceptions, this hypersensitivity was to one or more strains of streptococci, subgroup A of the beta streptococci and the alpha group being the most important.

Although the difference is of questionable significance, patients with nongranulomatous uveitis showed a greater incidence of active foci of infection (55%) than did patients with granulomatous uveitis (28%).

Patients with nongranulomatous uveitis showed a greatly decreased incidence of systemic evidence of granulomatous disease (10%) as compared with patients with granulomatous uveitis (78%). This indicates that nongranulomatous uveitis is not related to an underlying granulomatous disease.

The specific intravenous administration of a Streptococcus vaccine to hypersensitive patients with nongranulomatous uveitis gave a successful result in approximately 80% of such patients who were adequately treated. This successful result is manifested by apparent desensitization of the hypersensitive patient and a remission of further attacks of uveitis.

This evidence supports the hypothesis that nongranulomatous uveitis is an allergic reaction, usually dependent on a bacterial allergy to streptococci, and tends to establish nongranulomatous uveitis as a sound clinical entity, with a demonstrated pathogenesis.

SUPERFICIAL PUNCTATE KERATITIS

Isolation of a Virus

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IOWA CITY

SUPERFICIAL punctuate keratitis is a confusing term which has been applied to numerous superficial changes in the cornea. Fuchs [1] first used the term to describe the corneal changes associated with epidemic keratoconjunctivitis. Since then nearly any type of change in the corneal epithelium and superficial layers of the cornea has been classified by this description. One of us (A. E. B.)[2] attempted to differentiate the virus types of keratitis and suggested that the disease was of virus origin. At that time we had isolated a virus in one of the cases, but we had not had sufficient experience to be sure that the virus was the cause of the disease. Thygeson [3] has given a full clinical description of 26 cases and a well-prepared differential diagnosis. In this paper, we are discussing a similar clinical entity, although the clinical course in some of our patients has been somewhat variable. We have followed nine patients with the disease over a period of four to eight years.

CLINICAL DISEASE

The clinical disease is similar to that recently described by Thygeson [3] It is a bilateral keratitis characterized by epithelial and subepithelial opacities (Fig. 1). The opacities are centrally located on the cornea and appear to be more numerous on the upper half. Each opacity is irregular in shape, although roughly oval in the vertical axis, and consists of tiny white or gray dots. This gives the opacity a stippled appearance. The centers of the opacities stain irregularly with fluorescein. The lesions are best observed with the biomicroscope, with which they appear to be essentially in the epithelium. There is no evidence of conjunctivitis, and cultures of the conjunctiva rarely yield bacteria. The bulbar conjunctiva occasionally shows a slight injection of the larger blood vessels. However, an almost uniform hyperemia of the blood vessels extends from the superior rectus down to the upper limbus (Fig. 2).

The disease has normal remissions, and the lesions on the cornea come and go rapidly. During the attack there may be a dozen or more spots on the cornea, while during a remission one or two spots may be seen on the portion of the cornea pro-

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1. Fuchs, E.: Keratitis Punctata Superficialis, Wein. klin. Wchnschr. **2**:837, 1889.
2. Braley, A. E.: Virus Diseases of the Cornea, M. Rec. & Ann. **44**:102, 1950.
3. Thygeson, Phillips: Superficial Punctate Keratitis, J. A. M. A. **144**:1544, 1950.

tected by the upper lid. The corneal sensitivity is usually slightly decreased, but may be normal. The Schirmer test shows normal or increased lacrimation. There is sometimes a slight foamy material at the lateral and medial canthi, which appears to be Meibomian secretion due to the increased blinking. Vision is disturbed and variable. Usually it is reduced to 20/30 or 20/40; however, during the attack it may

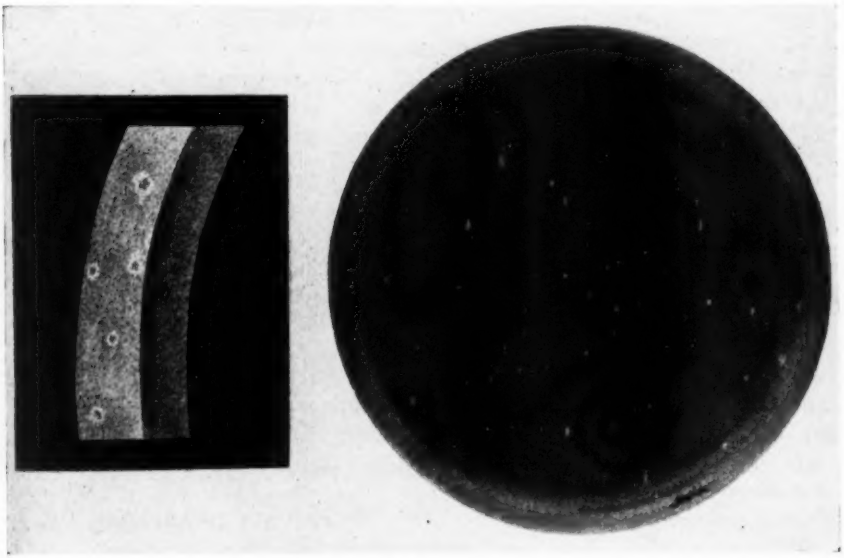

Fig. 1.—Superficial punctate keratitis.

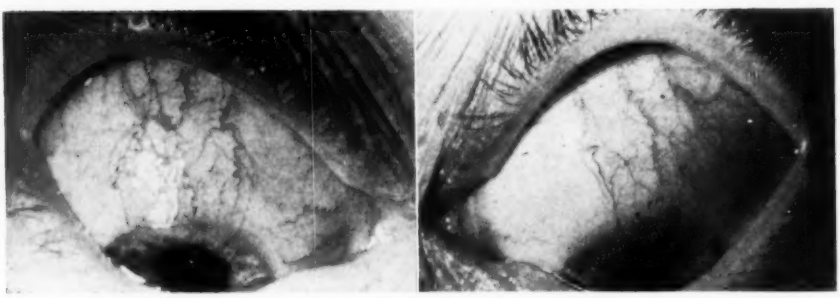

Fig. 2.—Congestion of the conjunctival blood vessels.

be reduced to 20/100. During the remission the acuity is normal. There is no vascularization of the cornea, although during an attack there may be hyperemia of the limbal loops.

The symptoms may be mild or rather severe, as they occur in individual patients. The commonest symptoms are burning of the eyes, excessive tearing, and blurred vision. During an attack, seeing halos around lights is a common symptom. Excessive blinking and foamy discharge in the eyes are also complaints. Nearly all the patients

are nervous, impatient persons, who frequently appear to be psychoneurotic. We feel sure that this condition is often overlooked because the patients present so many features of psychoneurosis.

The lesions on the cornea are easily missed during a remission, even with the slit-lamp microscope, since during this period the only lesion will be hidden by the upper lid. The life cycle of these lesions is shown in Figure 3. The lesion begins as a tiny epithelial fleck, which looks like a crust or tiny piece of fuzz in the normal corneal film. It does not disappear by blinking, however. This fleck grows somewhat irregular, but becomes oval, with the long axis vertical. The lesion measures about 0.2 mm. in length and 0.1 mm. in width. The center of the lesion may fall out,

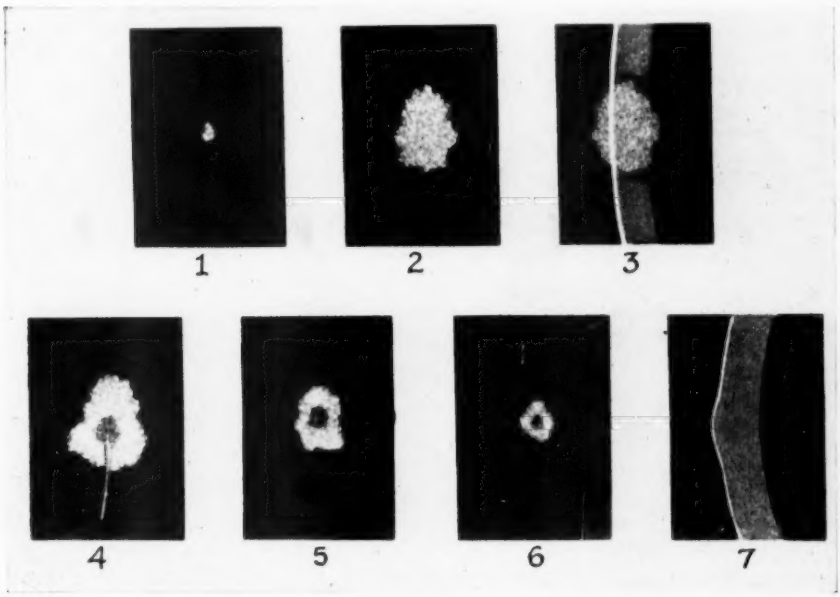

Fig. 3.—Cyclic development of the corneal lesions.

or a tiny filament may be formed by a roll of epithelium. This may remain several minutes to an hour, but is usually knocked off by the upper lid a few moments after it is formed. A small area of fluorescein staining remains in the center of the lesion. The fleck then begins to disappear and grow smaller as the epithelium heals. The opacity disappears, but leaves a small hump in the apparently normal corneal epithelium that may persist for several hours. During an attack these lesions may be watched. Some may require only 12 hours to appear and disappear, while in others the stage following the filament formation may persist for a week or more. The bilateral distribution is shown in Figure 4. There is a wide variability in the appearance of the corneal film, which at times appears thick and viscous and at other times so thin it is detected with difficulty. During the attack the corneal film may be absent.

METHODS OF INVESTIGATION

Scrapings of the cornea were taken daily with a small platinum spatula and used immediately to inoculate a tissue culture, which consisted of serum ultrafiltrate, balanced salt solution, and embryo mouse brain.[4] Each tissue culture was handled in a different manner. Five corneal scrapings were taken from one patient (GM). Prior to the taking of the scrapings and subsequently, at intervals, blood was drawn.

The tissue cultures were incubated at 37 C. for 12 to 48 hours; then intracerebral inoculations were made in five white Swiss mice (Rockland stain). The mice were watched carefully for evidence of encephalitis. As they became ill, their brains were removed and transmitted into either tissue culture or other mice. The first corneal scraping did not produce encephalitis in the inoculated mice; but the second and fifth scrapings produced an encephalitis which could be transmitted to tissue culture and other mice. The incubation period in mice varied somewhat during the original isolation of the virus but averaged about two weeks.

Isolation of the Virus.—An agent which could be transferred from mouse brain to tissue culture or to other mice was established. When each brain was removed, a small piece was

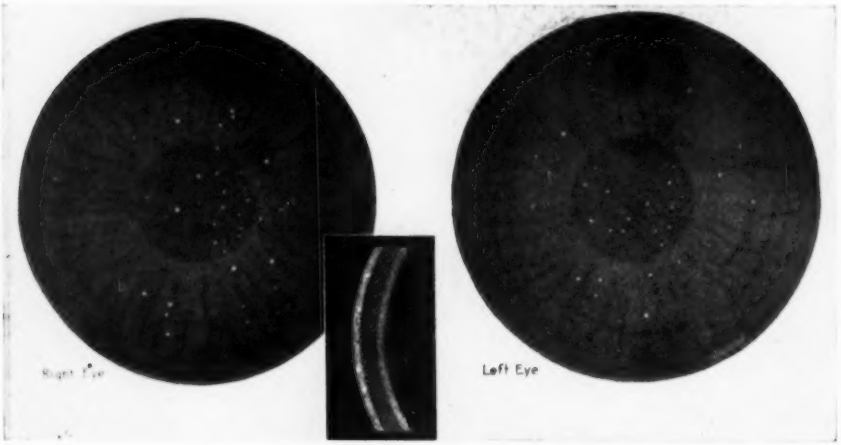

Fig. 4.—Bilateral distribution of the corneal lesions.

placed in nutrient broth. This broth was placed in incubation at 37 C. No bacteria could be demonstrated either in subculture or on smear preparation of the broth. The broth remained clear, with a small bit of brain floating in the liquid. The rest of the mouse brain was placed in a sterile steel-ball mill and ground. Then, 3 cc. of balanced salt solution was added. The mixture was pipetted off into a centrifuge tube. The material was then centrifuged at low speed to take out the larger pieces of brain. With the supernatant material other mice and tissue culture were inoculated. After six passages a virus was established which would produce an encephalitis in all mice inoculated, with an incubation period of seven to 9 days. The virulence increased until by mouse-to-mouse passage a dilution factor of 10^{-5} could be obtained with a minimal lethal dilution of $10^{-4.5}$. From tissue culture the minimum lethal dilution was $10^{-2.5}$.

Rabbit Cornea Inoculation.—After a definite agent had been established in mouse brain material, it was used to inoculate the rabbit cornea. Several linear scratches in the corneal epitheilum were made with a No. 24 hypodermic needle. Mouse brain obtained from inoculated mice was removed and suspended, as described above, and the material smeared on the scarified rabbit cornea. The corneal epithelium was healed in 24 hours, and no signs of inflammation were produced until the 8th day, when it was noticed that whitish-gray lines appeared on the inoculated cornea (Fig. 5). These lines consisted of tiny opacities which were similar to the

4. Braley, A. E.: Epidemic Keratoconjunctivitis, Tr. Am. Acad. Ophth. **48**:153, 1944.

clinical disease. The opacities changed from day to day, but those which stained with fluorescein persisted for approximately a week. At no time was there evidence of inflammation in the eye. The conjunctival blood vessels were not injected, and there were no signs of irritation of the iris. The opacities disappeared entirely and had not returned after approximately six weeks. These opacities developed in two of four rabbits inoculated. The other eye of the rabbit, which was similarly inoculated with sterile normal mouse brain, did not exhibit any corneal changes.

At present the virus does not produce corneal changes in rabbits, since it has been passed through many mouse passages and has been stored for long periods at low temperatures. The virus produces a mouse encephalitis and will grow in tissue culture, and patients with the disease still show neutralizing antibodies to the virus. However, it does not appear to be any longer capable of producing the corneal disease in rabbits.

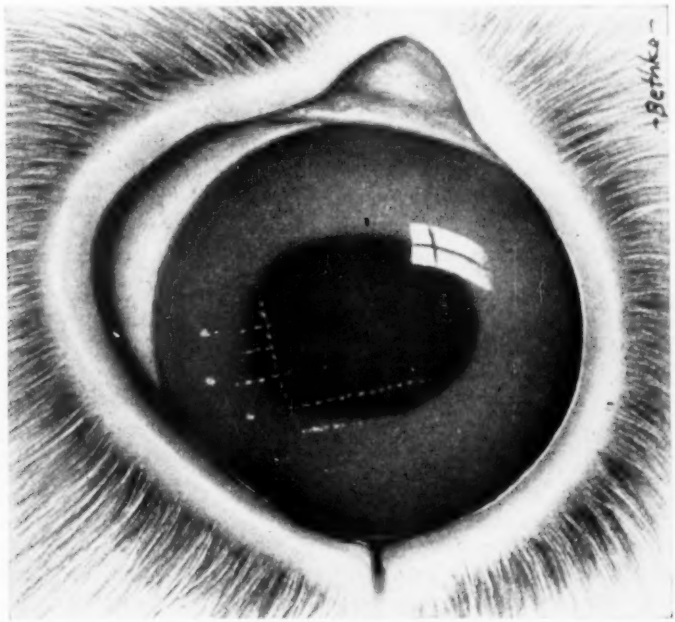

Fig. 5.—Experimental disease in rabbits.

NEUTRALIZATION STUDIES

Blood serum drawn from one of the patients at the time of the corneal scrapings was used in neutralization tests against the newly isolated virus. To make these tests, we used the same method as for neutralization tests in epidemic keratoconjunctivitis.[4] Neutralization tests on the patient showed a wide variation in the blood serum. At the time the virus was isolated, there was only a suggestion of neutralizing antibodies in the circulating serum. However, at the end of a week there were approximately 1,000 neutralizing substances, as previously reported for epidemic keratoconjunctivitis. As the patient experienced a remission, neutralizing antibodies in the serum gradually increased. Blood was drawn from this patient at monthly intervals over a long period. So long as there was a remission, the neutralizing antibody titer in the serum was high, but as the titer began to drop, a

few corneal opacities would appear. These would increase as the drop occurred, so that there was a wide variation in individual patients.

Blood was studied from all nine patients having the disease. Many of the patients, particularly those who had persistent attacks that did not show remissions, had only a suggestion of neutralizing antibodies. One of these patients is most interesting. She showed a suggestion of neutralizing antibodies which persisted and did not vary. She had many corneal opacities in both eyes; and, although new ones developed, many of the old ones remained stationary over long periods. Eight of the nine patients had neutralizing antibodies which seemed to fluctuate with the remissions of the disease. One patient, however, never had any neutralizing antibodies so far as we could demonstrate, although he had the typical clinical picture.

In order to determine whether the virus was allied to herpes simplex virus or some of the other known viruses, known herpes immunization serum was also mixed with the virus. There was no cross immunization. However, on occasion a patient whose cornea appeared to present some herpes would show slight evidence of neutralization to this virus. Lymphocytic choriomeningitis and Tyler's immune mouse serum were also used. Neither of these showed any neutralization of the virus. We concluded from the cross immunization studies that the virus was undoubtedly a new one, but possibly closely related to herpes simplex in some respects, particularly to the clinical disease. Patients with only labile herpes did not have neutralizing antibodies to this virus.

A population study of 56 patients with various ocular diseases was made in order to determine the number of antibodies present in the normal population. This study was most confusing in that 17 of the 56 subjects showed some neutralizing antibodies. Most of the patients who had neutralizing antibodies had nonspecific types of uveitis. At present it is impossible to say why the patients with uveitis had neutralizing antibodies to the disease; we were never able to isolate the virus from fluid of the anterior chamber of any of these patients with uveitis.

SKIN TESTS

Mouse brain material was gathered from mice which died with the disease. These brains were carefully ground in a ball mill and mixed with 13 cc. of isotonic sodium chloride solution per mouse brain. This was designated as the 10^{-2} dilution. The material was then centrifuged at low speed and used to inoculate mice to be sure that we had the viable virus in the brain suspension. The fine suspension was then heated at 56 C. in a water bath for 12 to 24 hours. After this heating process the intracerebral inoculation of the mice failed to produce encephalitis.

The material was then injected intracutaneously in 0.1 cc. amounts in patients with the disease and in many patients without it. After intracutaneous inoculation of the material a slight area of redness develops in some persons, but this is usually gone within a few minutes and does not produce any erythema, redness, or reaction in the normal skin. In patients with the disease there is a wide variation in the amount of local reaction produced. Most patients during the attack of the disease show a mild reaction. The reaction to a skin test was considered positive when there was an area of induration of approximately 1.5 to 2.0 cm. The site of inoculation was usually elevated and reddened, and remained red and indurated for 72 hours to five days. Occasionally an area of induration remained for seven days. It was not

always possible to predict, in patients with the disease, whether there would be a positive skin reaction. The positive skin reaction was usually present during an attack of the disease and might be only mildly positive during the remission.

All the 17 patients who had some circulating antibodies showed slightly positive reactions to the skin test.

FILTRABILITY OF THE VIRUS

Although final size of the virus cannot be accurately determined at present, the virus readily passes through a number of filters. It readily passes through two pads of Seitz filter and has been filtered through a number of collodion membranes. The virus must be very small, possibly in the neighborhood of 50 to 60 mμ, because it passes filters with an average pore size of 100 mμ. It does not, however, pass filters with an average pore size below 50 mμ.

INCLUSION BODIES

Smears of scrapings from the corneal epithelium were studied with the Giemsa stain. So far as one of us (A. E. B.) could determine, there were no demonstrable changes in the corneal epithelium cells. The epithelial cells were entirely normal, although there was some variation in their staining characteristics. It was impossible for us to distinguish between the normal epithelium and the cells that were undoubtedly infected with the virus.

Touch preparations were made from mouse brain. These were meticulously studied for inclusion bodies, but none could be demonstrated. The mouse brain was sectioned in paraffin and stained with hematoxylin and eosin. At the site of inoculation with the brain there was usually considerable reaction. The reaction was almost entirely lymphocytic, although there was considerable perivascular infiltration of lymphocytes, as well as polymorphonuclear leucocytes. These infiltrations were widespread in the brain. In some of the larger brain cells there was a suggestion of eosinophilic intranuclear inclusions; however, these were so variable that it was impossible to determine their exact nature. No cytoplasmic inclusions could be demonstrated on section. Further investigation along this line will be necessary.

It must be concluded, however, that no definite inclusion bodies are formed.

EFFECT OF KILLED VIRUS ON THE PATIENT'S DISEASE

Seven of the nine patients were treated with intradermal and subcutaneous inoculations with the killed virus. There was a wide variation in the reaction to this method of therapy. The first patient responded quickly with a high serum antibody response, which went up to 10,000 neutralizing doses and has remained at that high level since. He received only five intradermal inoculations of the killed virus. He has had no attacks of the disease in five years.

The second patient (Fig. 3) received the vaccine for three years, during which time she had attacks approximately every two months. On administration of more than 0.2 cc. of the mouse brain preparation a slight local reaction occurred, together with a new crop of corneal opacities. We tried increasing the amount of vaccine at two-week intervals, and at each inoculation of 0.5 cc. or more there would be a distinct flare-up, usually within 24 to 48 hours after the inoculation. The patient's serum antibody titer also showed considerable variation during this period. She was placed on a regimen of 0.2 cc. of mouse brain suspension every two weeks. This

was not followed by a flare-up, and she has been entirely free of corneal opacities for two years.

None of the other five patients received any beneficial effect. It seemed that each time we gave the killed vaccine the patient would respond with an acute flare-up in the eyes. All five patients became discouraged and have stopped the therapy voluntarily.

One patient, however, has continued therapy in spite of the absence of effect. When first seen, his serum antibody titer was very questionable, and it was doubtful whether he had any antibodies. However, after repeated small doses of vaccine, his serum antibody titer has gradually increased, but we have never been able to get more than a bare suggestion of antibodies in his serum. Clinically he has the same disease, but it has been impossible to be sure that he is getting any antigenic response from the local disease in the eye.

OTHER THERAPY

All these patients have been treated with many agents. None of the antibiotics or chemotherapeutic agents are of any use. Many of the patients have had their corneas curetted and cauterized with iodine. When the corneal epithelium heals and the eye quiets down after this therapy, there is an immediate recurrence of the disease. Aureomycin, oxytetracycline (Terramycin), chloramphenicol (Chloromycetin), and bacitracin have not changed the course of the disease, and five patients report that local therapeutic agents increase rather than decrease their symptoms. One of the patients had improvement with local use of cortisone. Two showed a pronounced increase in the number of corneal opacities. At present we are unable to explain the good results with cortisone therapy.

COMMENT

Superficial punctate keratitis is a disease which is limited to an inflammation of the cornea. From one patient with the disease, after repeated corneal scrapings, it was possible to isolate a virus. This virus produced a similar disease in rabbits after corneal inoculation. Patients with the disease have circulating antibodies which appear to increase with remissions and decrease with attacks. The virus is difficult to isolate because of the presence of antibodies, and repeated daily corneal scrapings must be taken, possibly during a period when the antibody titer is low. Once the virus is isolated, it is extremely stable. With mouse inoculations it has a titer of $10^{8.5}$. The virus appears to be very small, perhaps between 50 and 60 mμ in diameter. No definite inclusion bodies have been demonstrated. However, it is suggested that intranuclear inclusions may be present. The killed virus produces a slightly positive skin reaction in patients with the disease. When the killed virus is used in therapy, the results are unpredictable. Some patients may respond quickly, while others may not respond at all.

Local medication is not beneficial, but cortisone should be given a trial.

SUMMARY

Superficial punctate keratitis is presumably a virus disease.

The virus may be associated with other diseases.

Therapy of the disease is unsatisfactory.

SCLEREDEMA ADULTORUM

Ocular Manifestations

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SCLEREDEMA adultorum, first described by Buschke [1] (1900, 1902), is a rare systemic disease characterized by generalized nonpitting edema of the body unassociated with fever, loss of weight, or much evidence of illness. It is preceded by an acute infection, usually respiratory, and of streptococcal origin. There follows an asymptomatic period, varying from a few days to several months, although occasionally there may be a prodrome of malaise, myalgia, and low-grade fever. Then begins a pale, firm swelling of the skin, commencing as a rule at the nape of the neck and referred to by the patient as a "stiff neck." It spreads to the face, chest, trunk, and abdomen, and, to a less extent, the extremities. The evolution of edema is rapid, being sometimes a matter of only two or three weeks. A slow regression commences soon, which may take from one to eight months. Isolated patches or islands of edema may persist as long as 30 years. Recurrence is not uncommon, sometimes after many years, but recovery is usually without sequelae. The systemic nature of the disease is exemplified by patients exhibiting pleural, pericardial, peritoneal, or joint effusion (Vallee,[2] 1946; Leinwand,[3] 1951). The prognosis is good.

Over 100 cases have been described, and a number of excellent reviews have appeared (Epstein,[4] 1932; Touraine, Golé, and Soulignac,[5] 1937; Sweitzer and Laymon,[6] 1938; O'Leary, Waisman, and Harrison,[7] 1940; Vallee [2]). Although the age range is from birth to the seventh decade, approximately 50% of the cases reported occurred during childhood and adolescence; hence the name is misleading.

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From the Department of Ophthalmology, Post-Graduate Medical School of New York University-Bellevue Medical Center.

1. Buschke, A.: (*a*) Vorstellung eines Falles von Sklerödem vor der Berliner Gesellschaft für Dermatologie, Arch. Dermat. u. Syph. **53**:383, 1900; (*b*) Über Sklerödem, Berl. klin. Wchnschr. **39**:955, 1902.

2. Vallee, B.: Scleredema: A Systemic Disease, New England J. Med. **235**:207, 1946.

3. Leinwand, I.: Generalized Scleredema: Report with Autopsy Findings, Ann. Int. Med. **34**:226, 1951.

4. Epstein, N.: Scleredema Adultorum (Buschke), J. A. M. A. **99**:820, 1932.

5. Touraine, A.; Golé, L., and Soulignac, R.: La cellulite sclérodermiforme extensive bénigne: 1. Sclérœdème de Buschke, Ann. dermat. et syph. **8**:761, 1937.

6. Sweitzer, S., and Laymon, C.: Scleredema Adultorum (Buschke), Arch. Dermat. & Syph. **37**:420, 1938.

7. O'Leary, P.; Waisman, M., and Harrison, M.: Scleredema adultorum, Am. J. M. Sc. **199**:458, 1940.

Twice as many females were affected as males. The manifestations of the disease have been of interest chiefly to dermatologists and internists. Ocular involvement in scleredema has been reported only once in the ophthalmic literature (Stenbeck,[8] 1940).

The present case and a review of the literature suggest that involvement of the eye and adnexa is not uncommon.

REPORT OF A CASE[9]

P. P., a white woman aged 45, was admitted to the eye service of this institution in February, 1952, for study of persistent bilateral chemosis of the conjunctivae.

In several previous hospitalizations for scleredema, elaborate laboratory and clinical studies had shed no light on the nature of this curious disease. Extraction of all the patient's teeth in January, 1944, had been followed immediately by a socket infection. About one month later, a pale, firm, nonpitting edema had begun in the neck and spread to the face, chest, back, and extremities, but not to the hands or feet. Facial edema was extreme, with swollen lids and conjunctival chemosis. Her previous history revealed a partial thyroidectomy in 1924.

Besides the generalized edema, physical examination in 1944 revealed evidence of bilateral hydrothorax, pericardial effusion, and ascites; the kidney and liver functions were normal; the basal metabolic rate ranged from —2 to —9%; serologic reactions were negative; the blood chemistry was within normal limits, and 17-ketosteroid determinations were normal. Biopsy of skin from the breast was reported as showing a picture consistent with a diagnosis of scleredema adultorum. A slit-lamp examination of the cornea was reported as revealing a normal condition.

Treatment with a variety of agents accomplished little. The patient received large doses of desiccated thyroid, without effect. Anterior pituitary extract, effervescent urea, and mercurials produced some diuresis. Fever therapy proved most effective in obtaining dehydration. By July, 1945, her skin had gradually returned to normal, although the conjunctivae remained swollen and the face somewhat puffy.

This situation persisted for the next seven years, until the present admission. Physical examination then revealed no abnormalities other than diffuse enlargement of the left lobe of the thyroid and fluctuating hypertension (220/110 to 120/80). There was no edema of the skin, although her face was puffy, or evidence of hypothyroidism. The ocular findings were of unusual interest.

Ophthalmological Study.—Vision was 20/20 in each eye, with correction.

The lids were puffy but not indurated. A slight ptosis of the left eyelid was present (Fig. 1).

The lower bulbar conjunctiva was markedly chemotic in both eyes, being slightly more injected in the left eye than in the right. The color of the conjunctiva was pale gray, with a faint amber tint. Few conjunctival vessels were seen. The conjunctiva ballooned out from the limbus temporally, nasally, and inferiorly (Fig. 2). The upper conjunctiva lay flat against the sclera. Traversing the edematous tissue were many clear, branching, and coiled tubular channels, extending from the limbus to the fornices (Fig. 3). A few were seen in the flat, upper conjunctiva. The channels occupied the subepithelium and the deeper layers of the conjunctiva. In optical section (Fig. 3) the conjunctiva presented a Swiss-cheese appearance, similar to the illustrations of chemosis in biomicroscopy texts. However, the channels retained their identity during and after manipulation with a spatula and moved with the conjunctiva. At no time did they contain blood.

The caruncles were glistening and edematous.

The palpebral conjunctiva contained a few blebs.

Vital staining of the conjunctiva with azure II was more intense in the chemotic portions of the bulbar and palpebral conjunctiva, which took a diffuse punctate stain, with occasional clumps. The channels did not take the dye.

Although corneal sensitivity was normal and the patient had no complaints, there was a superficial punctate keratitis in the limbal zone of each eye, extending from 9 to 3 o'clock. These

8. Stenbeck, A.: Über einen Fall von Sklerödem mit Augenveränderungen, Acta ophth. **18**:76, 1940.

9. This patient was previously reported as Case 3 by Vallee.[2]

Fig. 1.—Facies of patient. Note puffy lids and chemosis.

Fig. 2.—Chemotic conjunctiva.

areas stained with fluorescein and even more markedly with azure II, whereas the upper portion of the corneas took only a faint stain with the vital dye. The involved area corresponded to the extent of chemotic conjunctiva.

The irises showed normal configuration and reactions.

Gonioscopic examination revealed a normal wide angle with an occasional tiny vessel traversing it.

Punctate nuclear and cortical opacities of coronary type were observed in the lens of each eye.

The vitreous was clear.

The disks, fundus vessels, and maculas were normal.

Extraocular muscles were normal except for slight ptosis of the left eyelid.

The visual fields were normal.

Intraocular tension was normal.

The pathological report on a biopsy specimen of chemotic conjunctiva was as follows: "A section of fibrous tissue is almost covered with squamous epithelium. The stroma is slightly

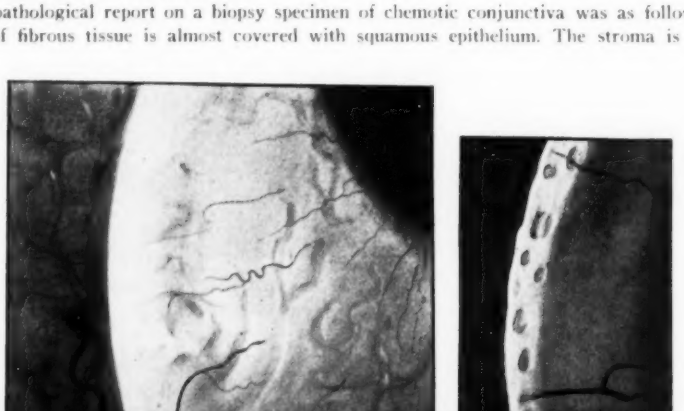

Fig. 3.—Chemotic conjunctiva (optic block) and section showing dilated channels (lymphangiectasia).

edematous. It contains many empty, endothelium-lined channels. There are two or three minute subepithelial clusters of lymphocytes [Fig. 4]." These dilated channels are probably lymphatics in a state of lymphangiectasia.

Periodic-acid staining was negative for metachromatic substance; however, the tissue examined was unsatisfactory, and no more could be obtained.

The status of the blood-aqueous barrier was determined by the fluorescein test of Amsler and Huber. The substance entered the anterior chamber after six minutes, indicating no increase in capillary permeability.

PATHOLOGY OF SKIN IN SCLEREDEMA

Characteristic changes involve the dermis. These consist of perivascular infiltration, thickening, and loosening of collagen bundles, which are separated by clear spaces. Vessels and hair follicles are also surrounded by clear spaces. When stained with Cresylechtviolet (Freund,[10] 1930), the tissue stains blue-gray, and the spaces

10. Freund, H.: Über Sklerodem (Buschke), unter besonderer Berücksichtigung der Histologie, Arch Dermat. u. Syph. **161**:92, 1930.

take a brilliant red. The latter stain, for metachromatic substance, probably reveals mucopolysaccharides (hyaluronates). The staining reactions, however, vary at different stages of the disease (Epstein [4]).

Fig. 4.—Photomicrograph of biopsy specimen of conjunctiva. Note numerous endothelium-lined channels.

PATHOGENESIS OF SCLEREDEMA

Buschke [1b] believed that the initial infection (usually streptococcal) damaged the lymphatics, producing an elephantiasis of the skin. The conjunctival channels in the present case may represent just such a conjunctival elephantiasis. O'Leary and associates,[7] however, did not report any morphological disturbance of the lymphatics. Many other theories have been advanced, implicating such conditions as trophedema

(Helfand,[11] 1938), collagen toxin (Sellei,[12] 1928), pituitary disturbance (Freund[10]), endocrine disorders (Ehrmann and Brünauer[13]), and myxedema (O'Leary and associates[7]). Of special interest is the occurrence of a similar mucopolysaccharide in the localized form of myxedema (Epstein,[4] 1932; Watson and Pearce,[14] 1950), but there are no significant alterations of the basal metabolic rate in scleredema. Leinwand[3] classified scleredema among the collagen diseases.

The most intriguing suggestion was proposed by the author of the stress theory, Hans Selye[15] (1944). He described experiments on mice in which estrogens applied to the skin produced a peculiar, turgid edema of the skin and subcutaneous tissues which grossly and microscopically resembled scleredema adultorum. Histochemical methods revealed a metachromatically staining polysaccharide in the tissue. Selye stated his belief that scleredema might represent a response to stress in which the initial infection elicits the alarm reaction with an outpouring of adrenocortical steroids, related to the estrogens, producing the edema. Further evidence along this line may be seen in the work of Duran-Reynals and associates[16] (1950) on macaques, in which a peculiar, turgid edema of the sex skin occurs at estrus. He was able to duplicate this edema by the use of estrogens. The edema could be made to disappear with use of either gonadotropins or hyaluronidase. It was shown that the swelling was based on the accumulation of hyaluronates in the tissue. Histological sections showed large vacuoles containing metachromatically staining polysaccharides (hyaluronates).

CLINICAL STUDY OF CASE

Three methods of clinical study were employed:

1. In an effort to determine whether the disease could be related to an endocrine disturbance, estrogens were applied locally to the arms by rubbing, following Selye's procedure in mice (estradiol in sesame oil to one arm; a sesame oil control to the other). After a week of daily applications, no change in the skin was noted. Then 1 cc. of estradiol was injected subcutaneously in the thigh, without effect.

2. Since the condition might be based on a disturbance of the ground substance of the mesenchyme (hyaluronates), the patient was given hyaluronidase (Wydase) topically—300 turbidity-reducing units per cubic centimeter, one drop every hour to the right eye. Although the patient thought there was greater ease in movement of the eye after two days of the treatment, the edema did not appear to be altered. The cornea, however, showed less punctate staining.

Hyaluronidase was next injected subconjunctivally in the right eye (75 turbidity-reducing units in 0.5 cc.). After one hour there was no decrease of edema.

11. Helfand, M.: Scleredema Adultorum (Buschke): Its Relationship to Trophedema and Its Pathogenesis, Arch. Dermat. & Syph. **37**:809, 1938.

12. Sellei, J.: Sklerödema adultorum (Buschke) (Induratio progressiva benigna sub cute), Dermat. Ztschr. **54**:161, 1928.

13. Ehrmann, S., and Brünauer, S.: Sklerödema adultorum (Buschke), in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Springer-Verlag, 1931, Vol. 8, Pt. 2, p. 875.

14. Watson, E., and Pearce, R.: Cutaneous Mucopolysaccharides in Localized (Pretibial) Myxedema, Ann. New York Acad. Sc. **52**:1004, 1950.

15. Selye, H.: Effect of Folliculoid Hormones on Abnormal Skin: Further Observations of Effect of Estradiol on Skin of Mice of Rhino, Hairless and Naked Strains, Arch. Dermat. & Syph. **50**:261, 1944.

16. Duran-Reynals, F.; Bunting, H., and Van Wagenen, G.: Studies on the Sex Skin of Macaca Mulatta, Ann. New York Acad. Sc. **52**:1006, 1950.

After several minutes of massage through the lids, however, the conjunctiva lay flat against the sclera, although the tubular channels persisted in two bunches, at the nasal and at the temporal portion of the limbus. This phenomenon illustrates the observed fact that pressure is an important factor in producing the effects of hyaluronidase (Hechter,[17] 1950). Whereas previously the conjunctiva had been firm and could not be manipulated readily, at the time of examination it exhibited loose, redundant folds, which could be picked up. The effect disappeared after a few hours, with a return of the previous edema. Repeated injections were all followed by this temporary action.

3. Cortisone was injected subconjunctivally and produced marked aggravation of the edema, which persisted three days. This confirms other clinical reports of an apparent antihyaluronidase action of cortisone (Seifter and associates,[18] 1950) and supports the theory of Selye.[15]

Although the results of the foregoing studies were inconclusive with regard to treatment, it must be remembered that the patient was in a late phase of the disease—it should be worth while to pursue this therapeutic approach in an early, fresh case.

The action of hyaluronidase and the histochemical findings suggest that scleredema adultorum may be based upon a systemic disturbance following infection which produces an alteration in the ground substance of the mesenchyme (accumulation of hyaluronates). This alteration may be mediated by estrogens or other adrenocortical steroids. Secondary disturbances of lymphatics may also occur.

OCULAR MANIFESTATIONS REPORTED IN SCLEREDEMA

Stenbeck [8] described exophthalmos, edema of the lids, and chemosis in the right eye in a 66-year-old woman, followed shortly by similar involvement of the left eye, with loss of vision in each eye. The patient died, and autopsy revealed extensive connective-tissue replacement in the orbits. The validity of the diagnosis in this case has been criticized (Vallee [2]). Stenbeck stated that ocular complications had been known to occur in only three previous cases, these being (1) infiltration of the lids; (2) transient diplopia and intermittent mydriasis, and (3) scleredema following irradiation of an orbital sarcoma.

A cursory survey of the literature reveals, however, numerous examples of involvement of the ocular adnexa, consisting of edema of the lids and/or conjunctiva. These changes were present in the first case described by Buschke.[1a] Similar findings were reported by Vallee,[2] in three out of four cases; by Epstein [4]; Guy and Amshel [19] (1934); Frank [20] (1937); Oliver [21] (1938); Hoffmann [22] (1927), and Adler [23] (1926). The last author described a case in which edema of the lid was the only sequel of the disease and persisted for 30 years. O'Leary and

17. Hechter, O.: Mechanisms of Spreading Factor Action, Ann. New York Acad. Sc. **52**:1028, 1950.

18. Seifter, J.; Warter, P., and Fitch, D.: Preliminary Observations on Antiarthritic Effect of 21-Acetoxypregnenolone, Proc. Soc. Exper. Biol. & Med. **73**:131, 1950.

19. Guy, W., and Amshel, F.: Scleredema, Arch. Dermat. & Syph. **29**:777, 1934.

20. Frank, L.: Scleredema Adultorum (Buschke): Report of Case Involving Tongue, Arch. Dermat. & Syph. **36**:1052, 1937.

21. Oliver, E.: Scleredema Adultorum, Arch. Dermat. & Syph. **37**:694, 1938.

22. Hoffmann, E.: Das Krankheitsbild des Sklerödema (Skleremia) adultorum (Buschke), Med. Klin. **23**:392, 1927.

23. Adler: Sklerödem vor 30 Jahren, Zentralbl. Haut- u. Geschlechtskr. **20**:259, 1926.

associates,[7] however, in reporting on 15 patients, stated that the eyelids were not usually swollen. Many authors refer to a diffuse involvement, producing a mask-like facies.

The ocular manifestations of scleredema, therefore, consist of edema of the lids and conjunctiva. Trophic corneal disturbances, as in the present case, might be observed if looked for. The peculiar lymphangiectasia appears to be a unique lesion. Intraocular involvement rarely or never occurs.

DIFFERENTIAL DIAGNOSIS

Scleredema suffers from an unfortunate similarity in name to scleroderma, and the literature is filled with erroneous classifications of cases. There is little actual similarity between the two diseases. Early diffuse scleroderma may be confused with scleredema, but in the former there may be prodromal articular and vasomotor signs, waxy sheen, and sclerodactylia, and, later, atrophy, hide binding, and pigmentation. Biopsy reveals a different lesion, and the prognosis is poor.

Dermatomyositis has a febrile course, with muscular weakness, tremor, erythema, tenderness, and edema of the skin. Atrophy occurs, and the prognosis is poor.

Myxedema may closely resemble scleredema; however, it is characterized by changes in basal metabolic rate, elevated blood cholesterol, dry scaly skin, involvement of the hands and feet, and therapeutic response to thyroid. Nevertheless, histochemical similarities do exist between the two diseases involving the hyaluronate-hyaluronidase relationship.

Other edemas, such as lymphedema, angioneurotic edema, trophedema, and cardiorenal edema, must be ruled out.

Sclerema neonatorum is a disease of marantic infants, with dehydration and severe constitutional symptoms. It is another example of unfortunate terminology, since scleredema is sometimes called sclerema.

Subcutaneous fat necrosis may bear a vague resemblance to scleredema but has a different history and course.

TREATMENT

There is no effective treatment; the condition runs its course, and the prognosis is good. Fever therapy and use of radiant heat are of some benefit.

SUMMARY

Scleredema adultorum is a rare systemic disease, benign and self-limited, and characterized by generalized nonpitting edema. It may present the ocular complications of edema of the lids and conjunctiva, which may persist after the general manifestations are gone.

A case of scleredema adultorum is described, with chronic edema of the lids and conjunctiva of eight years' duration. A peculiar type of lymphangiectasia was present in the conjunctiva. In addition, there was a secondary, trophic corneal disturbance (superficial punctate keratitis).

Experimental correlations are described which suggest that the disease may be due to a systemic disturbance following an initial infection, which produces a change in the ground substance of the mesenchyme, the alteration being mediated by estrogens or related adrenocortical steroids.

3 E. 66th St. (21).

HEMAGGLUTINATION TEST OF MIDDLEBROOK AND DUBOS IN OCULAR TUBERCULOSIS

MAX FINE, M.D.
AND
MILTON FLOCKS, M.D.
SAN FRANCISCO

ALTHOUGH the clinical diagnosis of ocular tuberculosis is a fairly frequent one, a positive clinical diagnosis is not common. With the exception of such pathognomonic lesions as a conglomerate tubercle of the uveal tract, miliary tuberculosis of the choroid, tuberculosis of the conjunctiva in which biopsy or the finding of tubercle bacilli leaves no doubt of the etiological agent, or the hypersensitivity type of lesion in which a definite focal reaction to the injection of tuberculin occurs, the diagnosis of ocular tuberculosis is usually presumptive. It is generally made on the basis of a clinical picture of a chronic granulomatous disease in the eye when other causes of such disease are believed to have been ruled out. The presence or absence of various forms of supporting evidence, such as hypersensitivity to intradermal injection of tuberculin, calcified lymph nodes, or healed pulmonary lesions, may be used to shade the diagnosis toward "possible" or "probable," but in the strictest sense diagnoses which are not positive are presumptive only. Nevertheless, the true incidence of tuberculosis of the eye is such as to make accurate diagnosis an important problem. The increasing recognition of other causes of granulomatous disease of the eye during the past two decades has made the problem even more difficult, while emphasizing the presumptive character of the diagnosis of ocular tuberculosis in previous years. Brucellosis, sarcoidosis, toxoplasmosis, histoplasmosis, coccidiomycosis, and other granulomas have replaced tuberculosis as a diagnosis in many of the cases which would have been considered typical of the disease a few years ago. In this paper, the clinical, rather than the histological, diagnosis of ocular tuberculosis is meant, although it is not rare for the pathologist, given a lymph node for examination, to express difficulty in differentiating tuberculosis and sarcoidosis.

In the absence of a better laboratory test for support of the diagnosis, the intracutaneous tuberculin test is widely used. Its value is extremely questionable, for several reasons: (*a*) It gives no indication of the degree of ocular sensitivity; (*b*) a large percentage of the general population give a positive reaction; (*c*) it may be dangerous, particularly in cases in which establishment of the diagnosis is especially important. The attitude of most ophthalmologists in this country toward

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the intradermal test has been that a negative or a weakly positive reaction has no significance, whereas a high degree of cutaneous sensitivity tends to support the diagnosis of ocular tuberculosis.

Woods's [1] studies of cutaneous sensitivity in patients with both clinically and histologically diagnosed ocular tuberculosis revealed little parallelism between the cutaneous sensitivity and the intensity or character of the ocular lesion. Of his series of 270 patients with a clinical diagnosis of ocular tuberculosis, 43% were sensitive to 0.001 mg. of old tuberculin U. S. P. and 14% to 0.1 mg. The results were strikingly similar in 21 cases of ocular tuberculosis diagnosed histologically. On the other hand, 29% of nontuberculous controls were sensitive to 0.1 mg. of old tuberculin.

The occurrence of focal reactions in the eye following the skin test is common knowledge. As has been previously stated, these reactions have been accepted as one of the positive methods of establishing the diagnosis of ocular tuberculosis. The literature [2] contains numerous references to the very serious ocular reactions which have followed the injection of tuberculin.

HEMAGGLUTINATION TEST OF MIDDLEBROOK AND DUBOS: REVIEW OF THE LITERATURE

In 1948 Middlebrook and Dubos[3] described a hemagglutination reaction between sheep erythrocytes treated with a polysaccharide fraction of extracts of the tubercle bacillus and the sera of tuberculous patients. They claimed a high degree of specificity for the reaction, in contrast to earlier attempts at immunologic tests for tuberculosis. The test was performed in serial dilutions of the patient's serum. Heterophile agglutinins were removed by adsorption with untreated sheep red blood cells. Two controls were run—a suspension of treated sheep cells in saline solution and a suspension of untreated cells in patient's serum.

On the basis of theoretical considerations and the results of early trials, they suggested that a positive reaction in a 1:8 dilution could be considered presumptive evidence of tuberculous infection.

Gernez-Rieux and Tacquet,[4] in 1949, performed the Middlebrook-Dubos test on rabbits after injecting them intravenously with various strains of tubercle bacilli, virulent, and avirulent. All had strongly positive hemagglutination reactions on the 8th day after injection, the titer being highest on the 19th day. The highest titers were obtained when the injected organism was of the same strain as that used to prepare the sheep cells, whether virulent or not. They applied the test to

1. Woods, A. C.: Influence of Sensitivity and Immunity on Ocular Tuberculosis, Pennsylvania M. J. **46**:1133-1138, 1943.

2. Woods,[1] Weizenblatt, S.: Allergic Ocular Reaction to the Tuberculin Test: Bilateral Cyclitis and Neuroretinitis, Arch. Ophth. **41**:436-443, 1949. Muncaster, S. B., and Allen, H. E.: Bilateral Uveitis and Retinal Periarteritis as Focal Reaction to Tuberculin Test, ibid. **21**:509-511, 1939. Linhart, W. O.: Induced Ocular Tuberculosis: Report of a Probable Case, ibid. **46**:271-276, 1951.

3. Middlebrook, G., and Dubos, R. J.: Specific Serum Agglutination of Erythrocytes Sensitized with Extracts of Tubercle Bacilli, J. Exper. Med. **88**:521-528, 1948.

4. Gernez-Rieux, C., and Tacquet, A.: Sur une réaction spécifique d'agglutination d'hématies sensibilisées, et sur son application au diagnostic de la tuberculose humaine, Bull. Acad. nat. méd. **133**:556-558, 1949.

138 patients and obtained a positive response in dilutions of 1:8 or over in 82% of 95 patients with active pulmonary tuberculosis. None of their 43 control patients gave positive reactions in a dilution as high as 1:8.

Sohier,[5] in 1950, used purified tuberculin antigen and found that 19 of 140 normal young adults gave a positive hemagglutination reaction (in a dilution of 1:8 or higher) and that 9 of 17 patients with active tuberculosis gave negative reactions. He concluded that on the whole his results were satisfactory.

Of special interest was the observation of Rothbard, Dooneief, and Hite[6] that in 10 of 120 patients with active tuberculosis whose sera were tested monthly the hemagglutination reaction became negative, together with absence of activity of the disease and disappearance of tubercle bacilli from the sputum and gastric contents. It was their conclusion that the hemagglutination reaction had become more practical with the demonstration that old tuberculin can be substituted as the antigen for sensitization of sheep red blood cells for the special filtrates used by Middlebrook and Dubos. They believed that the test not only was specific but appeared to indicate the degree of tuberculous activity.

Smith and Scott[7] studied the test in 104 patients with active tuberculosis, in groups of patients with positive and negative tuberculin tests, and in healthy medical students before and after having had a tuberculin test. They concluded that the test is not a measure of clinical activity. A further observation was that patients with active tuberculosis and a good prognosis usually have positive tests. In far-advanced disease with a poor prognosis, the test is usually negative, possibly because an excess of antigen produced by the rapidly multiplying bacilli neutralizes the circulating antibodies. In cases of arrested tuberculosis the hemagglutination test is usually negative, because insufficient antigen is available to stimulate antibodies. From studies on subjects with positive skin tests and negative hemagglutination tests, they concluded that the antibodies apparently disappear gradually after a subclinical primary infection.

Fleming, Runyon, and Cummings[8] tested the sera of more than 400 patients with the Smith and Scott modification of the hemagglutination test for tuberculosis. They found that sera of normal persons usually had no titer or low titers, but that a few had high titers. Patients with active tuberculosis had higher titers than patients with inactive disease, but extremes of titers were found in both groups. The highest average titer was in the group with far-advanced tuberculosis. In a small group of patients followed over a long period, there was no definite correlation of the effect of treatment with trends of titers. Sera of 22 patients with proved sarcoidosis yielded titers which were similar to the normal groups in their distribution and in their low average. They concluded that with the old tuberculin antigen the test is of limited clinical value. Elevation of titer is suggestive of

5. Sohier, R.: Réaction d'hémagglutination, type Dubos Middlebrook réalisée avec une tuberculine purifiée: Résultats obtenus, Ann. Inst. Pasteur **78**:283-285, 1950.

6. Rothbard, S.; Dooneief, A. S., and Hite, K. E.: Practical Application of a Hemagglutination Reaction in Tuberculosis, Proc. Soc. Exper. Biol. & Med. **74**:72-75, 1950.

7. Smith, D. T., and Scott, N. B.: Clinical Interpretation of the Middlebrook-Dubos Hemagglutination Test, Nat. Tuberc. A. Tr., pp. 77-84, 1950.

8. Fleming, J. W.; Runyon, E. H., and Cummings, M. M.: An Evaluation of the Hemagglutination Test for Tuberculosis, Am. J. Med. **10**:704-710, 1951.

tuberculosis in cases in which the differential diagnosis includes this disease. A negative titer does not rule out the presence of active tuberculosis.

Kirby, Burnell, and O'Leary[9] found that 9% of 251 patients with nontuberculous disease had a titer of 1:8 or over, while 57% of patients with active tuberculosis had titers of 1:8 or more. They concluded that the test is of little practical aid in the diagnosis of pulmonary tuberculosis because conventional methods of diagnosis are more accurate.

In Adcock, Haley, and Davey's[10] series, 17.1% of 256 normal patients had a titer of 1:8 or over, as compared with 84.0% of patients with active tuberculosis. They concluded that it is doubtful whether the test as it now stands is of any value as a diagnostic procedure or as an index of activity of disease.

Young and Leonard,[11] in a clinical evaluation of the test in 547 persons, found that 79% of 83 patients with pulmonary tuberculosis had titers of 1:8 or more; that 16, or 84%, of 19 patients with nonpulmonary tuberculosis had titers of 1:8 or over, and that 26% of 411 healthy subjects had similar positive titers. They drew the following conclusions: 1. The test is of value chiefly in excluding tuberculosis. Patients who are not severely ill and whose serum contains no hemagglutinins, or hemagglutinins in a low titer, usually do not have active tuberculosis. 2. A titer of 1:8 or higher is only suggestive of the disease. They stated:

> The hemagglutination reaction is similar to the tuberculin skin test in that both indicate the presence of an active or arrested tuberculous lesion; however, the hemagglutinins usually decrease and may disappear when the disease becomes arrested, while the skin usually remains hypersensitive indefinitely.

Belz, Sohier, Bouchel, and Juillard,[12] applied the test in a study of 99 patients with ocular disease. They divided their patients into three groups: those with a presumptive diagnosis of tuberculosis, those who were possibly tuberculous, and those who were not tuberculous. Of the patients with a presumptive diagnosis of ocular tuberculosis, 67% had a hemagglutination titer of 1:8 or higher, in contrast to 3% of the control group. The authors stated they are hopeful that this test may be of diagnostic and prognostic aid. They intend to continue the investigation as begun and also to study the reaction using aqueous humor instead of blood serum.

Bunn, Drobeck, Gino, and Adair[13] made extensive studies of the test in man and animals. They concluded that as a diagnostic tool and as a means of determining the course of the disease, the Middlebrook-Dubos test fails to be practicable. Among 428 patients representing routine medical admissions, of whom 66 had tuberculosis, they found a titer of 1:8 or more in roughly 80% of the patients with active tuberculosis and in 20% of the nontuberculosis patients. They compared the

9. Kirby, W. M.; Burnell, J. M., and O'Leary, B.: Evaluation of the Hemagglutination Reaction in the Diagnosis of Active Tuberculosis, Am. Rev. Tubere. **64**:71-76, 1951.

10. Adcock, J.; Haley, R. R., and Davey, W. N.: The Middlebrook Hemagglutination Test for Tuberculosis: An Evaluation in Normal Subjects and in Patients with Tuberculosis, J. Lab. & Clin. Med. **38**:736-741, 1951.

11. Young, R. M., and Leonard, W. A., Jr.: Clinical Evaluation of the Middlebrook-Dubos Hemagglutination Test, Am. J. Clin. Path. **21**:1045-1050, 1951.

12. Belz, A.; Sohier, R.; Bouchel, J., and Juillard, J.: La réaction d'hémagglutination type Middlebrook-Dubos dans les tuberculose oculaires: Premier résultats obtenus, Ann. ocul. **184**:586-605, 1951.

13. Bunn, P.; Drobeck, B.; Gino, J., and Adair, C.: Some Observations upon the Middlebrook-Dubos Hemagglutination Test in Man and Animals, Ann. Int. Med. **37**:84-95, 1952.

results of the hemagglutination test and the standard Mantoux test in the first 225 patients. In all categories more patients had positive tuberculin reactions than positive hemagglutination titers. In their experimental studies, two groups of rabbits were inoculated with virulent human tubercle bacilli, one group intravenously or intraperitoneally and the other intraocularly, and the variations in hemoagglutinin titers were studied weekly. Of the 8 rabbits inoculated intravenously, disseminated tuberculosis developed in all but two, but no predictable trend in the concentrations of the agglutinins from week to week was manifested. In contrast to the unstable trend of circulating hemagglutinins in disseminated rabbit tuberculosis, the agglutinins in ocular tuberculosis, which was strictly localized, were stimulated in a more equable manner. The majority of the 26 rabbits with ocular tuberculosis failed to show hemagglutinins until the fifth week of infection. Thereafter, with few exceptions, titers rose to a higher average than 1:32 and remained fairly constant at that level for seven months. In only four rabbits was there a significant drop from peak levels as time passed, and never was there a fall to a level below 1:8. The ocular disease did not parallel these levels; it usually reached a peak in two weeks, and the lesions began to organize by the fifth to the seventh week. Administration of streptomycin, corticotropin, or cortisone, although changing the clinical picture of the disease, did not alter the appearance or the subsequent height of the titers.

Despite the differences in clinical evaluation of the test expressed by the authors cited above, it is apparent that there is general agreement concerning the specificity of the test (Charts 1 and 2). Practically all observers report positive reactions in 75 to 90% of tuberculous patients. Apparently, healthy adults show positive titers in 9 to 26% of tests. The chief disagreement is whether the test may be used as an index of activity.

EVALUATION OF THE TEST IN OCULAR DISEASE

The hemagglutination test is being largely by-passed by the internists because of their relatively superior methods of diagnosis of pulmonary tuberculosis. Kirby, Burnell, and O'Leary [9] stated:

> The test was of little practical aid in diagnosis since m. tuberculosis could be readily demonstrated in the sputum of most of the patients with high hemagglutination titers, and positive reactions occurred in 10 per cent of persons with non-tuberculous conditions.

However, because of the difficulties of diagnosis peculiar to ocular tuberculosis and the previously mentioned inadequacies of the intracutaneous test, the hemagglutination test might be of considerable value to the ophthalmologists if it were proved useful in any or all of the following ways: (1) if it demonstrated the same degree of accuracy in the diagnosis of ocular tuberculosis as in that of pulmonary tuberculosis; (2) if it offered an index to the degree of activity of a tuberculous ocular lesion; (3) if it proved to be as good an index of sensitivity to the products of the tubercle bacillus as the Mantoux test, since it is performed in vitro and avoids the possible dangers of the intradermal test, and (4) if it could be used to differentiate tuberculosis and sarcoidosis in questionable cases.

The hemagglutination test for tuberculosis was performed on 101 consecutive patients with inflammatory ocular disease in an attempt to answer these questions. In each of these patients an etiological survey was made, consisting of a complete physical and ophthalmologic examination; dental, otorhinologic, and urologic

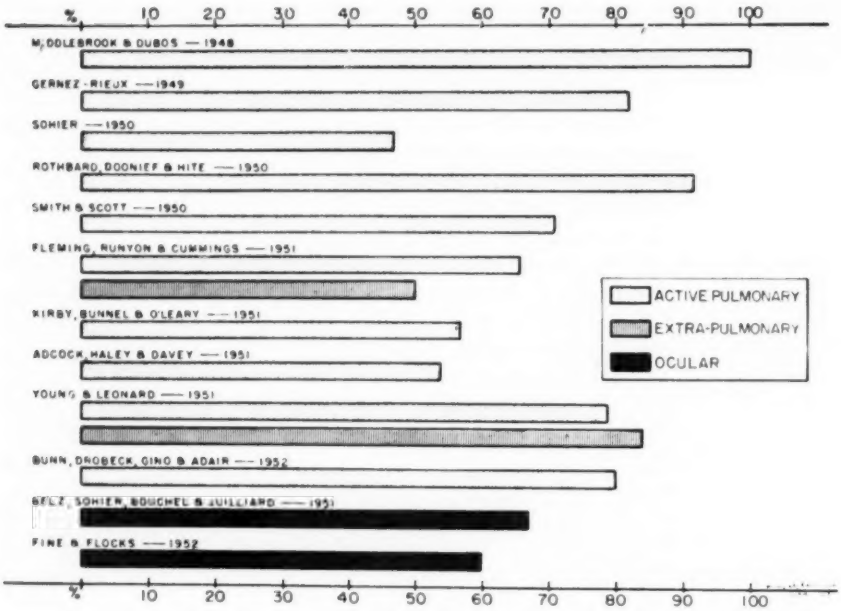

Chart 1.—Percentage of reactions with titers of 1:8 or over in patients with tuberculosis.

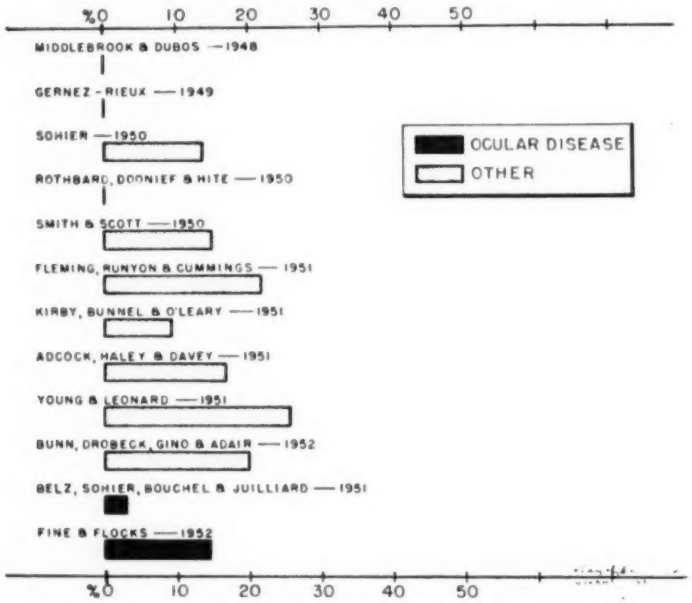

Chart 2.—Percentage of reactions with titers of 1:8 or over in patients with no evidence of tuberculosis.

examinations; urinalysis; complete blood cell count; determination of the sedimentation rate; Kahn test; agglutination test for brucellosis; Frei test; toxoplasmin test (if indicated); fasting blood sugar determination; roentgenologic studies of the chest, accessory nasal sinuses, teeth, and sacroiliac joints; roentgenologic studies of the long bones and skull (if indicated); hemagglutination test for tuberculosis (blood drawn before intradermal tuberculin test); Mantoux test (after blood has been drawn for hemagglutination test), and serum albumin and globulin determinations, when sarcoidosis is suspected.

Our bases for the clinical diagnosis of ocular tuberculosis were as follows: A positive diagnosis was made when tubercle bacilli could be demonstrated in the lesions, as in one case of primary tuberculosis of the conjunctiva, when phlyctenular keratoconjunctivitis was associated with the demonstration of tubercle bacilli in lymph nodes (Case 22), and when a focal reaction occurred in the eye after an injection of tuberculin. A presumptive diagnosis of ocular tuberculosis was made in cases of the following diseases: nodular iridocyclitis in which syphilis, sarcoidosis, and brucellosis could be ruled out; (*b*) sclerokeratitis or keratitis profunda in which syphilis was excluded and in which there was evidence of old or active pulmonary tuberculosis or hypersensitivity to tuberculin; (*c*) chronic or recurrent granulomatous uveitis with signs of old systemic tuberculosis or hypersensitivity to tuberculin in which other causes of granulomatous uveitis were not found; (*d*) chronic or recurrent granulomatous uveitis associated with retinal perivasculitis in which other causes of granulomatous uveitis were not found; (*e*) retinal periphlebitis associated with evidence of old systemic tuberculous infection or hypersensitivity to tuberculin, and (*f*) phlyctenular keratoconjunctivitis in association with healed pulmonary tuberculosis or a high degree of tuberculin hypersensitivity.

In the hemagglutination tests the modified procedure used by Smith and Scott [7] was followed except for two changes introduced by Rothbard, Dooneief, and Hite [6]: 1. The antigen was diluted 1:12 instead of 1:15. 2. Only a single absorption of patient's serum with 0.2 cc. of untreated packed, washed sheep erythrocytes in a water bath at 37 C. for 30 minutes was made.

METHODS AND MATERIALS [14]

Preparation of Washed, Packed Sheep Erythrocytes.—Sheep red blood cells stored in Alsever's solution were centrifuged for 10 minutes at 1,800 rpm, and the supernatant was removed with a pipette. These red blood cells were then washed three times with 6 vol. of isotonic sodium chloride solution. After the last washing, the cells were centrifuged for 20 minutes at 2,000 rpm, and as much of the supernatant as possible was removed with a small pipette. These cells were used in the test as "washed, packed cells."

Preparation of Antigen.—Old tuberculin of four times standard strength was diluted 1:12 in buffered isotonic sodium chloride solution, 0.5 ml. of tuberculin in 5.5 ml. of buffered saline solution being used. To this, 0.1 ml. of washed, packed red cells was added and incubated for two hours in a water bath at 37 C. The mixture was thoroughly shaken at approximately 15-minute intervals. This cell suspension was removed from the water bath and centrifuged at low speed (approximately 1,000 rpm for six minutes). It is desirable to use a low speed in order to avoid a hard button of red cells, which is difficult to resuspend without hemolysis of some of the red cells. The cells were washed three times with 6-ml. volumes of buffered saline and

14. The hemagglutination tests were performed in the clinical laboratory, Veterans Administration Hospital, San Francisco, under supervision of T. V. Feichtmeir, M.D., Director.

finally, resuspended in 50 ml. of buffered saline, to be used as antigen in hemagglutination tests. This antigen may be stored for three days at 4 C. temperature.

Absorption of Patient's Serum.—To 1.0 ml. of buffered saline was added 1 ml. of patient's serum; the solution was inactivated at 65 C. for three minutes, cooled to room temperature, and to it added 0.2 ml. of untreated packed, washed sheep erythrocytes; the mixture was incubated at 37 C. in a water bath for 30 minutes. The cells were removed from the serum by centrifugation at 2,500 rpm for seven minutes and discarded. This absorption of the patient's serum with normal red blood cells removed the heterophile antibodies, which are capable of agglutinating normal red blood cells. Absorbed serum may be stored indefinitely in a deep freezer without alteration of antibody titer to sensitize red blood cells.

Hemagglutination Test.—With standard-size Wassermann tubes and racks, tests were set up with absorbed serum in twofold serial dilutions. To the first and second tubes was added 0.4 ml. of the absorbed serum. Serial dilutions were made from the second tube through eight tubes, with equal volumes of buffered isotonic sodium chloride solution. To tubes containing 0.4 ml. of serum dilution there was added 0.4 ml. of 0.2% suspension of the sheep red blood cells being used as antigen, and to another tube, containing 0.4 ml. of 1:2 dilution absorbed serum, was added 0.4 ml. of a 0.2% suspension of untreated, washed sheep erythrocytes. A known positive and a known negative serum were included each time an unknown serum was tested. The negative sera were obtained from persons with negative cutaneous reactions to tuberculin.

The tubes were shaken and then incubated at 37 C. on a water bath for three hours. Upon removal from the water bath, the tubes were reshaken and left at room temperature overnight, to be read the following morning. Tests were read in a manner similar to that of the usual type of red blood cell agglutination.

In accordance with the position of a number of other investigators, a titer of 1:8 or higher was considered positive, and a titer of 1:4 or lower, negative.

RESULTS

The results of the hemagglutination tests are summarized in Tables 1, 2, and 3. In 25 patients a clinical diagnosis of ocular tuberculosis had been made before the results of the hemagglutination test were known. Of these, 15 (60%) had a positive hemagglutination test in a dilution of 1:8 or higher. The highest positive titer was 1:64. In 74 patients with similar diseases of the cornea, sclera, uveal tract, retina, and optic nerve diagnosed as nontuberculous, 11 (14.8%) had a titer of 1:8 or higher. The highest titer in this group was 1:128, in a patient with Reiter's syndrome. Five patients with granulomatous iridocyclitis due to sarcoidosis, verified by biopsy of lymph nodes or skin, all had negative hemagglutination tests. Two patients with active adult pulmonary tuberculosis and ocular disease not definitely tuberculous had positive hemagglutination tests (titers 1:8, 1:16) but were not included in the group with ocular tuberculosis because of the probability that the titers were produced by the pulmonary lesions. It was not possible to relate the height of the titer to the level of activity in our patients with ocular tuberculosis. Successive tests were made on the majority of these patients. The variation in titer was never more than one serial dilution and could not be considered significant except in confirming the reliability of the method.

No definite correlation could be made between the result of the hemagglutination test and that of the tuberculin skin test in our cases. Of all patients with positive hemagglutination tests, 45% had positive skin tests and 54% negative skin tests. The patient with the highest titer (1:128) on repeated tests had a negative skin reaction to 1:1,000 dilution of old tuberculin. The patient with the strongest skin reaction (positive to 1:1,000,000 dilution of old tuberculin) had a hemagglutinin titer of 1:8.

TABLE 1.—*Titer of Hemagglutination Test in Patients with Clinical Diagnosis of Ocular Tuberculosis*

Case No.	Diagnosis	Titer
1	Recurrent choroidoretinitis	1:8
2	Choroidoretinitis; nodular iritis; hemorrhage into vitreous	Neg.
3	Recurrent parenchymatous keratitis, bilateral	1:16
4	Retinal periphlebitis, bilateral; recurrent hemorrhage into vitreous	1:4
5	Chronic iridocyclitis; history of apical pulmonary lesion; hemoptysis	1:32
6	Chronic granulomatous choroiditis and iridocyclitis	1:16
7	Recurrent severe iridocyclitis; Ghon tubercle	1:32
8	Chronic granulomatous iridocyclitis, bilateral	1:64
9	Chronic granulomatous uveitis, bilateral	Neg.
10	Retinal periphlebitis, bilateral; recurrent hemorrhages into vitreous	1:8
11	Retinal periphlebitis	1:2
12	Chronic granulomatous choroiditis, R. E.	1:4
13	Recurrent disseminated choroidoretinitis, bilateral	1:4
14	Phlyctenular keratoconjunctivitis, recurrent; healed pulmonary tuberculosis	1:16
15	Chronic granulomatous iritis; retinal periphlebitis	1:64
16	Recurrent central choroiditis, R. E.	1:4
17	Chronic recurrent choroiditis, bilateral	1:16
18	Nodular iritis; disseminated choroidoretinitis, R. E.; retinal periphlebitis	1:4
19	Chronic granulomatous uveitis, R. E.	1:8
20	Deep keratitis, bilateral	Neg.
21	Recurrent central choroiditis, bilateral	1:32
22	Phlyctenular keratoconjunctivitis; tubercle bacilli demonstrated in axillary lymph node	1:16
23	Sclerokeratitis, tuberculous (active pulmonary tuberculosis found later)	1:32
24	Recurrent central choroiditis, tuberculous	1:4
25	Primary tuberculosis of conjunctiva (bacilli found)	1:64

TABLE 2.—*Titers of Hemagglutination Test in Patients with Clinical Diagnoses of Nontuberculous Ocular Disease*

Diagnosis	No. of Patients	Titers							
		Negative	1:2	1:4	1:8	1:16	1:32	1:64	1:128
Acute nongranulomatous iritis associated with rheumatoid disease	15	10	1	1	..	2	1	..	..
Acute nongranulomatous uveitis, other than rheumatoid	11	5	2	2	..	2	..	..	..
Chronic nongranulomatous uveitis	5	3	..	1	..	..	..	1	..
Chronic granulomatous uveitis, nontuberculous	4	2	1	..	..	1	..	..	..
Chronic cyclitis with cataract	4	4	..	..	..	..	..	..	..
Chronic choroiditis	4	3	..	1	..	..	..	..	..
Acute exudative choroiditis	4	2	2	..	..	..	..	..	..
Sympathetic ophthalmia	3	1	1	..	1	..	..	..	..
Optic neuritis	4	2	1	..	..	1	..	..	..
Keratitis and keratoiritis	7	3	3	1	..	..	..	..	..
Scleritis	2	1	..	1	..	..	..	..	..
Uveitis due to sarcoidosis (proved by lymph-node biopsy)	5	4	..	1	..	..	..	..	..
Pseudotumor of orbits	1	1	..	..	..	..	..	..	..
Reiter's syndrome	1	..	..	..	..	..	..	..	1
Harada's disease	1	..	..	1	..	..	..	..	..
Retinal detachment, inflammatory	2	..	1	..	..	..	1	..	..
Retinal degeneration	1	1	..	..	..	..	..	..	..

From the foregoing evidence, the following conclusions may be drawn:

1. The percentage of positive agglutination reactions is definitely and significantly higher in the group of patients with a clinical diagnosis of tuberculosis of the eye than in the group of nontuberculous patients with similar ocular disease.

2. In the five patients with proved Boeck's sarcoid the uniformly negative hemagglutination tests suggests that the test may be of value in the differential diagnosis of this disease.

3. The percentage of false-positive and false-negative reactions in this series was quite comparable to that obtained in studies of other types of tuberculosis.

COMMENT

It should be noted that our study, independently undertaken, is very similar to that of Belz, Sohier, Bouchel, and Juillard.[12] The results, too, are roughly parallel. Their findings and ours suggest strongly that the test gives the same

TABLE 3.—*Incidence of Positive and Negative Titers in Hemagglutination Test on Patients with Clinical Diagnosis of Tuberculous and Nontuberculous Ocular Disease*

Clinical Diagnosis	No. of Patients	Hemagglutination	
		Positive (Dilution 1:8 or Higher)	Negative
Ocular tuberculosis	25	15 (60%)	10 (40%)
Active pulmonary tuberculosis with ocular disease not definitely tuberculous	2	2 (100%)	0
Uveitis associated with Boeck's sarcoid	5	0	5 (100%)
Ocular disease, nontuberculous	69	11 (15.9%)	58 (84.1%)
Total nontuberculous ocular disease	74	11 (14.8%)	63 (85.2%)

response in tuberculosis of the eye as it does in tuberculosis elsewhere in the body. This is not surprising, for it is generally accepted that tuberculosis of the eye in humans is usually produced by hematogenous spread of tuberculosis from elsewhere in the body. A possible exception to this may be found in tuberculous retinal periphlebitis, for which there exists considerable experimental and clinical evidence that the spread to the retinal vessels occurs directly through the vitreous from other foci within the eye (ciliary body). However, this, again, presumes a previous hematogenous dissemination.

Because of the greater difficulties of diagnosis of tuberculosis of the eye, it is understandably more difficult to evaluate the accuracy of this laboratory test against the clinical diagnosis. It is these very difficulties in diagnosis, however, that make the test potentially more valuable in the diagnosis of ocular lesions than in the diagnosis of pulmonary tuberculosis. Further extensive clinical testing is necessary to ascertain the exact value of the test in the study of ocular tuberculosis. Unanimity exists on the specificity of the reaction, but the literature is conflicting concerning the relationship of agglutinin titer to the activity of tuberculosis. The evidence suggests that, unlike the skin test, the hemagglutination test tends to become negative in the absence of continued stimulation by the tubercle bacillus. Although this reduction in titer is not regular enough to be used to indicate the degree of

activity of the disease, it constitutes a great advantage over the skin test in that there is not the same high percentage of positive reactions in the general population.

In pulmonary, bone, and visceral tuberculosis, for which accurate laboratory and x-ray methods of diagnosis are available, the skin test is of some value in diagnosis, particularly in children, but the hemagglutination test, with its not inconsiderable number of false-positive and false-negative reactions, is of less value. In ocular tuberculosis, however, the situation is quite different. In view of (*a*) the impossibility of demonstrating tubercle bacilli in most cases; (*b*) the low degree of parallelism between ocular and cutaneous sensitivity, as pointed out by Woods; (*c*) the high percentage of positive skin tests in the general population, and (*d*) the danger of disastrous focal reactions from the use of the tuberculin skin test, we believe that the hemagglutination reaction is a safer and more valuable diagnostic test than the skin test in the diagnosis of tuberculosis of the eye.

Since its introduction, in 1948, by Middlebrook and Dubos,[5] the technique of the test has been simplified and improved, and work is now being done further to improve the test. Kirby and co-workers[9] stated:

> Attempts are being made to isolate fractions from this crude material [old tuberculin] which are relatively pure from a chemical standpoint and which may give greater specificity to the reaction. In addition, recent evidence indicates that the incorporation of complement into the system, with the recording of hemolysis rather than agglutination of erythrocytes, may give results which are more indicative of the presence of active tuberculosis infection.

Progress in the improvement of the hemagglutination reaction should be watched with great interest by the ophthalmologist.

SUMMARY

In a series of 101 patients with inflammatory ocular disease on whom an etiological survey was carried out, the hemagglutination reaction for tuberculosis was positive in a serum dilution of 1:8 or greater in 60% of patients whose disease was diagnosed clinically as ocular tuberculosis.

Five patients with Boeck's sarcoid, proved by biopsy, all had negative hemagglutination reactions.

The hemagglutination test appears to react with about the same degree of specificity in tuberculosis of the eye as it does in pulmonary tuberculosis.

Because of the relatively unsatisfactory methods available for the diagnosis of ocular tuberculosis, and the known inadequacies and dangers of the skin test in tuberculosis of the eye, it is suggested that the Middlebrook-Dubos hemagglutination test may be of considerable value in the diagnosis of tuberculosis of the eye and is worthy of further study.

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CHANGES IN SPECIFIC GRAVITY OF THE GROWING CRYSTALLINE LENS

A Technique for Investigation of Pathogenesis of Cataract

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AND
ROBERT H. PECKHAM, Ph.D.
PHILADELPHIA

A CATARACT may be defined as a loss of transparency of the crystalline lens, or an opacification occurring at any place in the lens or its capsule.[1] The mechanism for this opacification has been the subject of extensive research. Since the lens is a living, cellular organ, we may expect that changes in its protein structure are primarily involved in any alteration of its optical behavior. The optical properties of protein systems in general have excited only minor interest, as such data are of vital concern only in the cornea, lens, and vitreous body of the eye. It has been shown, however, that physical and chemical alterations of such proteins as muscle myosin, gelatin, and fibrin produce marked alterations in such optical properties as polarization of light, transparency, and absorption in various portions of the energy spectrum.[2]

It has been shown that the cornea owes its transparency to the arrangement of its fiber pattern and the chemical environment and composition of these fibers.[3] As would be expected, the cornea transmits visible light in a circularly polarized fashion.[4] This effect is increased when the fibers are placed under mechanical stress and is accompanied with opaqueness of the tissue. The fiber structure of the lens also produces polarization of light. If the lens is observed through crossed Nicol prisms, a Maltese cross is noted. If the lens is crushed lightly between the polarizers so as to rupture its fibers, it immediately becomes isotropic.[4]

Chemical alteration of protein systems, spoken of as "denaturation," also affects optical properties profoundly. It has been shown that the first change in protein denaturation is a liberation of sulfhydryl (–SH) and disulfide (–S–S–) groups in the protein molecule.[5] This primary phenomenon, although to some extent reversible, is followed shortly by irreversible chemical changes, which occur as a sequence of events, each depending upon the event just preceding and bearing no relation to the primary fault.

1. Town, A. E.: Ophthalmology, Philadelphia, Lea & Febiger, 1951, p. 292.

2. Chemistry of the Amino Acids and Proteins, edited by C. L. A. Schmidt, Springfield, Ill., Charles C Thomas, Publisher, 1938.

3. Hart, W. M., and Chandler, B. F.: The Cornea: I. Swelling Properties of the Fibrous Tunic of the Eye, Arch. Ophth. **40**:601-611, 1948; II. Factors Affecting the Transmission of Visible Light by the Fibrous Tunic of the Eye, ibid. **40**:612-623, 1948.

4. Hart, W. M., and Peckham, R. H.: Unpublished data.

5. Mirsky, A. E., and Anson, M. L.: Sulfhydryl and Disulfide Groups of Proteins: Methods of Estimation, J. Gen. Physiol. **18**:307-323, 1935.

It is of interest that lenticular changes resulting in experimental cataract have been shown to be presaged by a liberation of sulfhydryl groups from the lens as a primary change in all cases.[6] Subsequent alterations in hydration, electrolyte content, and pH may well be secondary events resulting from altered cell structure, such as the deposition of calcium, which occurs in any necrosis of tissue. These chemical changes dominate the picture in most considerations of the pathogenesis of cataract, but the mechanical effects of altered fiber structure, such as occurs in the cornea and other protein systems, must not be overlooked.

From the foregoing description we have a picture of cataract as a process in which physical and chemical events are combined in an alteration of protein structure known as "denaturation." Subsequent changes are part of a chain reaction which may mislead the unwary as to the primary defect.

The experimental inquiry to date has been fraught with two prime difficulties: (1) the failure to consider the lens as a growing tissue with a varying composition as a function of time, and (2) the focus of interest on the consequential chemical events in the cataractous lens. This situation can be corrected only by a careful study of the lens as a maturing organ and by a search for the point of departure which leads to the changes which we know as cataract.

PRESENT INVESTIGATION

Rats were chosen for such a study because they represent a standardized source of laboratory material in which the life span is compressed within convenient limits. They are cheap, easily cared for, easily bred, and, most important of all, have a constant gestation period of 21 days. Any of several attributes of the lens may be chosen for measurement in such a study—for example, weight, water content, volume, specific gravity, or electrolyte content. In the present study, specific gravity, weight, and water content were determined experimentally. Volume was obtained by calculation. Data on specific gravity only will be presented in this paper. It is our purpose to show how such data may be used for further investigation of the pathogenesis of cataract.

Methods.—A well-known strain of Wistar white rats was maintained in colony on a stock diet of commercial laboratory Checkers. No further supplementation was required to keep the animals in good nutritional state. Exact records were kept on dates of breeding, time of gestation, and date of birth.

The animals were weighed and killed by a blow to the occiput. Under a binocular dissecting microscope, a small incision at the limbus was made with a needle knife and the cornea removed with scissors. The zonule was separated with forceps and the lens lifted out in its capsule. Occasional adhering fragments of vitreous were removed with blunt forceps. The lens was transferred to a covered bottle for rapid weighing on an analytical balance and was then placed immediately in the gravity column for estimation of specific gravity.

Specific gravity was determined in a graded column of bromobenzene and kerosene, prepared according to the technique of Lowry and Hunter.[7] Equilibrium positions of standards and unknown (lens) were read with an Eberbach cathetometer at the 2-meter distance, the center of the cross hairs being placed at the center of the standard drop or lens being measured. A series of standards was prepared with sodium chloride. At the beginning of each experimental period, the linearity of the column was established by delivering a series of standard drops beneath the surface of the column and plotting the equilibrium positions of the standard drops against the known specific gravities. This curve then served for the graphic determination of the specific gravity of the lens. The accuracy of this method is ± 0.0002. Three separate compositions of the column were necessary to cover the large range of specific gravities encountered.

6. Bellows, J. G.: Cataract and Anomalies of the Lens, St. Louis, C. V. Mosby Company, 1944.

7. Lowry, O. H., and Hunter, T. H.: Determination of Serum Protein Concentration with a Gradient Tube, J. Biol. Chem. **159**:465-474, 1945.

The fact that the lenses reached a stable equilibrium in the column indicates that bromobenzene and kerosene did not penetrate the capsule at differential rates.

In determination of water content, lenses were dried to constant weight, *in vacuo*, in an Abderhalden desiccator.

Results.—Chart 1 shows the specific gravity of rat lenses plotted against the age of the lenses, expressed as the natural logarithm of time. Time is reckoned from the point of fertilization of the ovum. This correlation becomes possible because of the constant gestation period and the known time of breeding within a 12-hour period. Birth occurs at ln 3.02 (21 days after fertilization). The lower end of the curve may be extrapolated to zero time (point of fertilization) to give a value on the ordinate intercept which may serve as the theoretical specific gravity for primitive embryonic ectoderm. It is of interest that the lowest experimental values

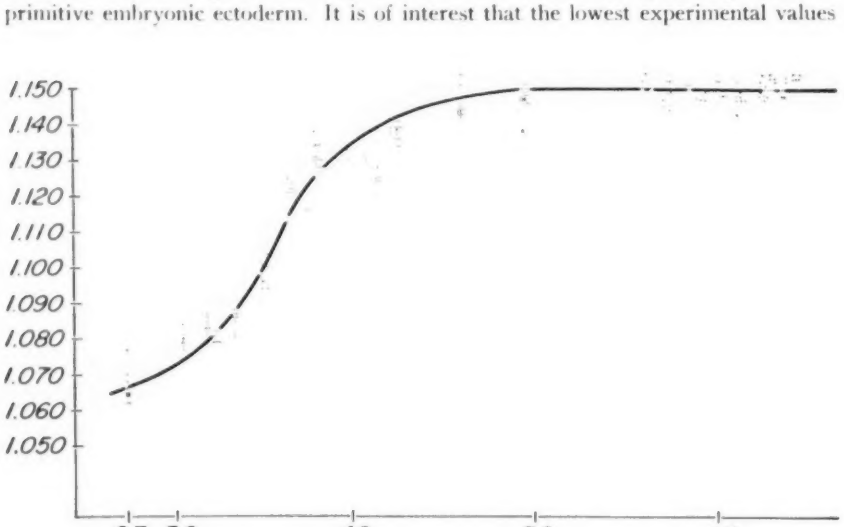

Chart 1.—Specific gravity of the rat lens plotted against the age of the lens, in days after fertilization, expressed as the natural logarithm of time.

obtained were about 1.050 in fetuses of 16 days postfertilization age. This value for specific gravity is of the order to be expected for blood and primitive mesenchymal tissue.

At 16 days after fertilization, the rat lens is a fluid-filled vesicle with a vascular net covering the capsule. The intracapsular substance of the lens remains fluid until about 30 days after fertilization (ln 3.5), when it begins to assume a semisolid character. It will be noted that it is at this time that the rapid rise of the curve begins.

The curve as a whole is indicative of a maturation process, which reaches its peak at about 5 log units (150 days after fertilization). Beyond this point there is no further increase in specific gravity with age. A gradual decline is to be expected in the aging lens.

It was felt that it would be of interest to compare this curve with the change in the amplitude of accommodation of the human lens which occurs as a function of age. Chart 2 shows the values for amplitude of accommodation, as given by Duane, plotted against the age of the lens, expressed in natural log units of time. This curve lacks sufficient data at the juvenile end. At the senile end, the curve may have been traduced by Duane for clinical convenience, inasmuch as the shoulder of the curve is atypical of a biological process. It is more probable that a gentler configuration is to be expected, as suggested by the dotted line. However, the general curve is seen to bear a striking similarity to Chart 1. Thus, it may be conjectured that decrease in plasticity of the lens is related to increase in specific gravity. In the early phases of development, this decrease in plasticity may be related to the gradual change from fluid to solid consistency and the elaboration of fiber pattern. In the more advanced phase of maturation, the accumulation of

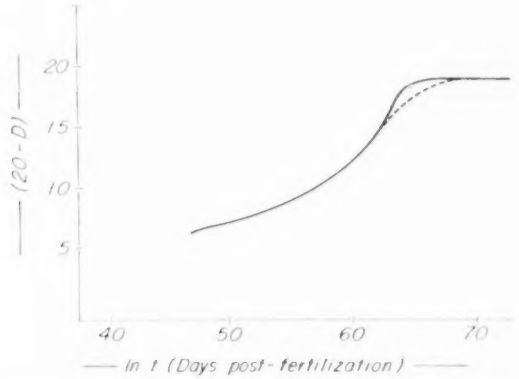

Chart 2.—Amplitude of accommodation of the human lens, as recorded by Duane, plotted against the age of the lens, expressed as the natural logarithm of time. A gestation period of nine months is assumed.

scleroprotein, commonly referred to as "sclerosis," may account for loss of plasticity. Both these processes, of course, lead to progressive decrease in the water-solid ratio, with a consequent increase in specific gravity.

COMMENT

It has been said that all persons would have cataract if they lived long enough. This statement implies that senile cataract is a result of maturation, i. e., a consequence of sclerosis. It remains to be determined, however, whether any form of cataract represents excessive maturation. Excessive sclerosis of the lens is often seen without visual impairment. Salit [8] contends that there are two kinds of sclerosis, physiologic and pathologic. This concept requires experimental affirmation.

8. Salit, P. W.: Water Content and Solids of the Cataractous and Sclerosed Human Lenses, Am. J. Ophth. **21**:755-762, 1938.

Future work calls for strengthening of the curve shown in Chart 1. It will then be of interest to produce experimental cataract by the various known means. If such cataracts are the result of premature maturation, the curve for specific gravity will be shifted to the left. Cataracts characterized by cortical liquefaction may show a precipitous rise of the curve with a sharp fall at the time liquefaction begins.

A similar study should be made on normal human autopsy material. Cataracts removed clinically may then be evaluated from this curve.

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CENTRAL AND PERIPHERAL FUSION

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IT SEEMS that Worth [1] considered fusion essentially as a mental process and made no distinction between the motor part of the fusion (the fusional movements) and the mental process of uniting two uniocular impressions into one single impression. This distinction was clearly indicated by Roelofs,[2] who also pointed out that binocular vision and fusion are different words to designate the same thing. Binocular vision is fusion, and this fusion should be differentiated into motor fusion (fusional movements) and sensory fusion, or the process of uniting the two retinal images into a unitary perception. The same distinction between motor and sensory fusion was recently stressed by Burian.[3] The work of Chavasse [4] has largely contributed to the present concept of binocular vision and fusion as reflexes, or, rather, as conditioned reflexes. This concept has been elaborated most completely along ontogenetic lines by Zeeman.[5]

When we apply this idea to fusion, it is convenient to keep in mind some simple definitions. A reflex is an action that results from stimulation without the aid of volition. A conditioned reflex involves the activity of cerebral associations. The unconditioned reflexes are sometimes called "congenital," the conditioned reflexes, "acquired." When we apply these definitions to fusion, we may again distinguish motor and sensory fusion. Sensory fusion cannot possibly be called a reflex; it is a perception:

> A perceptual process of considerable complexity made up of two distinct stages: a sensual image of considerable completeness is first elaborated by each uniocular mechanism contemporaneously, and these, if they are suitable, are then fused into one by a perceptual process on a higher level.[6]

This work has been supported by a grant from the Jan Dekker Stichting.

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1. Worth, C.: Squint: Its Causes, Pathology, and Treatment, Ed. 6, London, Ballière, Tindall & Cox, 1929.

2. Roelofs, C. O., cited in discussion at Strabismus Symposium, Ophthalmologica **110**:85 (July-Aug.) 1945.

3. Burian, H. M.: Place of Peripheral Fusion in Orthoptics, Am. J. Ophth. **30**:1005 (Aug.) 1947.

4. Chavasse, F. B.: Worth's Squint, or the Binocular Reflexes and the Treatment of Strabismus, Ed. 7, Philadelphia, P. Blakiston's Son & Co. 1939.

5. Zeeman, W. P. C.: (*a*) Strabismus Symposium, Ophthalmologica **110**:81 (July-Aug.) 1945; (*b*) cited by Keiner, G. B. J.: New Viewpoints on the Origin of Squint, 's Gravenhage, Martinus Nijhoff, 1951.

6. Duke-Elder, W. S.: Text-book of Ophthalmology, Vol. 1, London, Henry Kimpton, 1938, p. 1038.

Motor fusion, however, may reasonably be called a reflex, as in this case there is a reaction of the extraocular muscles to stimulation of a sense organ. It is generally accepted that fusional movements are reflexly excited by disparate identical images. In this sense motor fusion may indeed be compared to a conditioned reflex: It is the perception of the identical images which brings about the motor reaction intended to bring them on corresponding points of the retina.

Our understanding of fusion has been considerably amplified by the introduction of the concept of peripheral fusion. In 1939 Burian had shown by an ingenious method that peripheral identical stimuli may give rise to fusional movements, which are even capable of breaking up fusion maintained by central (foveal) stimuli.[7] During the war, without knowing of the work of Burian, I experimented with a different method and came to the same conclusions as Burian. The concept of peripheral fusion may influence our ideas of fusion in general and is especially suited to bring to light its reflex character.

Parsons[9] distinguished different stages in the course of the evolution of vision. The lowest, and most primitive, stage, which is essentially vital and utilitarian, he called "dyscritic." From it has evolved a more delicate, epicritic mechanism, susceptible of finer gradations and endowed with more accurate discrimination. The peripheral retina is endowed with some typical dyscritic properties. As such may, for example, be considered the appreciation of movement; there are, however, other properties on which depends the survival of the animal. These may be summed up as serving the purpose of primitive orientation in space. Roelofs[10] has presented a theory by which optic localization is explained. According to this theory, stimulation of a certain part of the retina not only produces a sensory effect but is also active in a motor sense. Simply expressed, stimulation of the retina gives rise to a sensory and a motor impulse. Roelofs considered this motor impulse the physiological correlate of localization. I have pointed out in a former article[11] that these motor impulses in general may produce the following physiological phenomena: a conjugate movement; a disjunctive, or fusional, movement; localization of the stimulus in space, and apparent movement. To it may be added the appreciation of movement. It is especially the peripheral retina which gives rise to these motor reactions. The "absolute," primitive dyscritic peripheral retina, if we could imagine such a thing as existing in man, would be active principally in a motor sense, while the sensory part might be nearly neglected. Central vision, on the contrary, is endowed with epicritic properties: It shows a high development of form and color sense; it serves the purpose of fine discrimination, appreciation of contours, etc. Motor activity is far less pronounced here, and it might even be

7. Burian, H. M.: Fusional Movements: Role of Peripheral Retinal Stimuli, Arch. Ophth. **21**:486 (March) 1939.

8. Winkelman, J. E.: De motorische component van de netvliesprikkel, Thesis, Amsterdam, 1946; The Significance of Peripheral Fusion, Ophthalmologica **115**:62 (Jan.) 1948.

9. Parsons, J. H.: An Introduction to the Theory of Perception, New York, The Macmillan Company, 1927.

10. Roelofs, C. O.: Die optische Lokalisation, Arch. Augenh. **109**:395, 1935.

11. Winkelman, J. E.: The Motor Impulse Elicited by the Retinal Stimulus and the Binocular Optical Reflexes, Brit. J. Ophth. **33**:629 (Oct.) 1949.

supposed that in the "absolute" fixation point, if such a point existed (Hartridge[12]), motor activity of retinal stimuli would approach zero.

In investigating binocular vision in squinters, we meet with considerable difficulty, caused by the fact that it is very hard for a person with normal binocular vision to understand the sensations and reactions of a person with defective binocular vision, and vice versa. This, in my opinion, is as difficult as for a normal and a color-blind person to discuss color. The only way in which to understand the sensations of squinters is to create circumstances in normal subjects which, in a way, may be compared with those in squinters. It is well known that in many cases of strabismus it is impossible to combine the retinal images into a single mental impression. In normal subjects a condition in which the retinal images cannot be united into a single mental impression can be brought about by using images giving rise to retinal rivalry, or rivalry of contours.

PRESENT INVESTIGATION

A test set-up was used similar to that described in two previous papers.[13] The subject sat in a completely darkened room 5 meters from an aluminized screen. Images intended for the fovea and for the periphery of each retina could be projected from a separate projection cubicle onto the aluminized screen. Dissociation of the images was brought about by Polaroid material and the use of suitable filters.

At first the two foveas only were stimulated by images giving rise to rivalry of contours. One fovea observed the image of a grating subtending a visual angle of about 3.5 degrees; the other fovea observed the image of a skull subtending a visual angle of about 2 degrees. The phenomenon of retinal rivalry was then observed, but on repetition it became very difficult to superimpose the two images, as the skull was constantly running out of the grating. It is evident that these dissimilar images of the foveas do not give rise to a fusional movement, intended to keep them on corresponding areas. Fusional movements of foveal images are possible only when they can be united into a single mental image.

Does the same rule hold good for peripheral images? The experiments were repeated for peripheral fusion, but with images giving rise to peripheral retinal rivalry. The fovea of each eye saw a small vertical luminous line; these lines were projected one above the other in a way that the subject saw them just in line. The peripheral retinal rivalry images were then suddenly projected in a way that they were imaged either on the temporal or on the nasal half of each retina. For this experiment the images of a grating and a skull were used, each subtending an angle of about 3.5 degrees. The peripheral images were projected to a distance of 40 cm. from the central images.[14] It was then seen, on exposure of the peripheral images, that the foveal images, which were in line, were displaced with regard to each other, indicating that the eyes had performed either a convergence or a

12. Hartridge, H.: The Visual Perception of Fine Detail, Philosophical Tr. Roy. Soc. London **232**:519, 1947.

13. Winkelman, J. E.: Projection Tachystoscope for Orthoptic Treatments: A Preliminary Report, Am. J. Ophth. **33**:461 (March) 1950; Peripheral Fusion, A. M. A. Arch. Ophth. **45**:425 (April) 1951.

14. Visual acuity at this region of the retina was sufficient to see the contours of the peripheral images.

divergence movement. This movement will not go so far as to bring the peripheral images on corresponding areas; therefore it would be indispensable that the images be similar, and that they could be united into one single image. When the experiment was repeated a few times, the phenomenon became less evident; probably the knowledge that the peripheral objects could not be united into one single image hindered the fusional reflex. Therefore never more than two trials were performed in one session and the experiment was repeated on a different day. The figure illustrates the test set-up. Subject W saw the grating and the lower line with the right eye, the upper line and the skull with the left eye. In this case the temporal half of each retina was stimulated by the peripheral objects. Subject L saw the upper line and the skull with the right eye, the lower line and the grating with the left eye. Here the nasal half of each retina was stimulated by the peripheral objects. Subject W had an esophoria of about 0.5 degree; Subject L, an exophoria of 1.5 degrees (Maddox test). The displacement of the lower line was noted in each case. In these experiments the lower line always went to the right after exposure of the peripheral objects. This indicated that the eyes of Subject W had performed a convergence movement, the eyes of Subject L, a divergence movement. If this movement went so far that the peripheral images were nearly superimposed, it was noted as + + +. A less extensive movement was noted as + +, and when the movement was evi-

The test set-up.

dent, but not exceeding about 1 degree, it was noted as +. No effect was noted as —. The results are tabulated.

Date	Subject W	Subject L
9/20	++	++
9/23	+++	+++
9/26	++	++
9/27	++	++
10/2	—	+++
10/10	+++	+++
10/16	+++	+++
10/17	+	+++
10/22	++	++
10/23	+	++

From this tabulation we may conclude that, with the exception of one observation on Subject W, exposure of the images giving rise to peripheral retinal rivalry was always followed by a fusional movement of the eyes.

This reaction is probably typical of the peripheral retina and, in my opinion, is in this case essentially a primitive reaction to light stimuli. When light stimuli fall on the temporal or the nasal half of each retina, motor impulses result which give rise to a fusional movement. It is not impossible that this reflex is present at birth and is responsible for keeping the eyes of babies straight. A similar suggestion was given by Hagedoorn [15] in view of the fact that the eyes of babies are

15. Hagedoorn, A.: Strabismus Symposium, Ophthalmologica **110**:73 (July-Aug.) 1945.

usually straight at birth, although the anatomical position of rest is one of divergence. He stated the opinion that this anatomical position of rest is probably corrected by another reflex, the fusion reflex, the anatomical apparatus of which must be present at birth. Recently Keiner[5b] investigated the sight of two newborn children before any optical stimulus had been able to act on the retina. With a 40-watt bulb at a distance of 1 meter, it was found possible to evoke in one of those babies "a conjugate fixation movement of very short duration." It is not impossible that this reflex is even present in squinters and that the findings of Burian[16] who proved that even patients with abnormal correspondence may react to peripheral stimuli with fusional movements, may be explained as constituting the remnants of this, probably congenital and unconditioned, reflex to light.

SUMMARY

In many cases of strabismus, it is impossible for the retinal images to be combined into a single mental impression. In normal subjects, a similar condition may be brought about by using images giving rise to retinal rivalry. When these images are observed haploscopically with the fovea of both eyes, retinal rivalry occurs, but after some time it becomes very hard to keep these images superimposed. When, on the contrary, the periphery of both retinas is stimulated by retinal rivalry images, a fusional movement may occur. This is considered as constituting a primitive reflex to light, possibly of congenital and unconditioned character.

16. Burian, H. M.: Fusional Movements in Permanent Strabismus: A Study of the Role of Central and Peripheral Retinal Regions in the Act of Binocular Vision in Squint, Arch. Ophth. **26**:626 (Oct.) 1941.

Clinical Notes, New Instruments and Techniques

INTRAVENOUS PENTOBARBITAL (NEMBUTAL) SEDATION IN EYE SURGERY

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EVEN BEFORE the days of general or local anesthesia it was the custom to give some sort of a sedative to a patient who was about to undergo operation. Although the agents employed at present are highly satisfactory, it is still not easy to predict the best dosage of an analgesic and hypnotic to be used in conjunction with local anesthesia. This is especially true in the case of the elderly, for whom an overdose must be avoided. Just as one cannot reason with a child, so it is sometimes difficult to do so when a person in his second childhood, and fairly heavy sedation must sometimes be used in order that the operation may proceed. Moreover, when the patient is already on the operating table, it may be too late to obtain adequate sedation.

The purpose of this paper is to present a method of sedation which is more accurate, and therefore more satisfactory, than that ordinarily used. It consists of the administration of a dilute solution of pentobarbital (Nembutal) sodium intravenously by the continuous drip method as soon as the patient is brought to the operating room and is usually continued throughout the procedure. The barbiturate is not a general anesthetic, for it is not given in anesthetic doses. The average amount given in this series of ophthalmic cases was slightly less than 2 grains (1.9 grains, or 0.124 gm.). As a rule, only meperidine (Demerol) hydrochloride, 50 to 100 mg., was given prior to operation by hypodermic injection.

The intravenous use of pentobarbital before or during surgical procedures is by no means new. Among the first to report it were Fitch, Waters, and Tatum,[1] in 1930; Carron[2] used it successfully in a series of 120 cases of the fenestration operation and in an additional 127 cases of various operations about the head and neck. He employed it in conjunction with nitrous oxide anesthesia. He stated that "by combining the hypnotic effects of intravenous pentobarbital sodium with the analgesic effects of endo-tracheal nitrous oxide, a minimum of both drugs is required." He first put the patient to sleep with pentobarbital, and additional doses were given during the procedure, as needed. He did not employ a continuous drip method.

Ausherman and Crawford,[3] in 1950, discussed the various uses of intravenous administration of pentobarbital. According to them, it is widely used, but few articles

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1. Fitch, R. H.; Waters, R. M., and Tatum, H. L.: Intravenous Use of the Barbituric Acid in Surgery, Am. J. Surg. **9**:112 (July) 1950.

2. Carron, H.: Nembutal in the Fenestration Operation, Anesthesiology **12**:465-469 (July) 1951.

3. Ausherman, H. M., and Crawford, O. B.: Uses of Pentobarbital Intravenously, Postgrad. Med. **8**:287-289 (Oct.) 1950.

have appeared in the literature. The purpose of their paper was to bring to our attention a successful method of complementing conduction anesthesia (topical, infiltration, regional, peridural, or spinal) by intravenous administration of pentobarbital. This barbiturate enhances the amnesic effect of narcotics given before operation and affords a degree of protection against untoward toxic reactions. It does not increase laryngeal reflexes, and these authors agree with others that it is less likely to cause laryngeal spasm than is thiopental sodium. Its great advantage is that one can put a patient to sleep during the operation, a state benefiting not only the patient but also the surgeon. High or low blood pressure and renal damage are contraindications.

Farquharson and Murphy [4] supplement nitrous oxide anesthesia with the intravenous administration of pentobarbital sodium and thiopental sodium. They prepare a syringe containing a mixture of 5 cc. of 5% pentobarbital sodium (0.25 gm.) and 20 cc. of 2.5% thiopental sodium (0.5 gm.). This mixture, of 25 cc., contains a short-acting and an ultra-short-acting barbiturate, which they used in 458 cases, the ages of the patients ranging from 18 months to 78 years. Its use was restricted to operations expected to last over two hours, and the barbiturates were used either for induction or for maintenance of anesthesia. The authors believe that liver damage constitutes a contraindication but that high blood pressure does not.

Coviello, Goldberg, and Robertazzi [5] use pentobarbital intravenously in combination with ethylene anesthesia; they have found that it is especially suitable for the very apprehensive, such as thyroid patients.

Several articles have appeared in the recent literature on the intravenous use of secobarbital (Seconal) in combination with nitrous oxide or spinal anesthesia.

Everyone fears surgery, especially when the eyes are concerned. The fear of the unknown may surpass the fear of the known, and even though most patients do not show it, they are under considerable emotional strain. To be sure, some are fatalistic and resigned, in which case very little sedation is required, but those who are emotionally upset require heavy sedation, and sometimes general anesthesia. Hypnotics sometimes fail to fulfill their purpose because they abolish whatever self-control the conscious mind imposes, exposing a primitive fright, such as is seen in children. In many cases it is possible to proceed with surgery by the intravenous use of pentobarbital sodium, when otherwise general anesthesia might have been required.

REPORT ON METHOD

Material.—Intravenous administration of pentobarbital sodium by the continuous drip method was used in a series of 80 cases of operations on the eye at the White Memorial Hospital and Clinic during 1952. In all these cases the usual forms of local anesthesia were used, topical or infiltration or both. The following types of eye surgery were performed: cataract extraction, 48; cyclodiathermy, 8; retinal reattchment, 5; iridectomy, 4; muscle operations, 4; excision of pterygium, 4; enucleation, 3; plastic surgery, 2; needling, 1; removal of intraocular foreign body, 1.

4. Farquharson, H., and Murphy, F. J.: Use of Pentothal Sodium-Pentobarbital Sodium Combination in Prolonged Surgical Procedures, Anesthesiology **11**:489-494 (July) 1950.

5. Coviello, V.; Goldberg, S., and Robertazzi, R. W.: Intravenous Pentobarbital Sodium-Ethylene Anesthesia, New York J. Med. **51**:1815-1818 (Aug. 1) 1951.

The ages of the patients ranged from 15 to 93 years. Of 80 patients, 8 were outpatients.

Procedure.—Twelve cubic centimeters of a solution of pentobarbital sodium (Nembutal sodium, Abbott), 50 mg. per cubic centimeter, was added to a 0.5 liter flask of isotonic saline. One will find, as a rule, that the amount of saline in this flask is not 500 cc. but very nearly 600 cc. This means that 600 mg. of pentobarbital sodium has been added to practically 600 cc. of isotonic saline, and each 100 cc. of this dilution will then contain about 100 mg. of pentobarbital sodium, approximately 1.5 grains. The flask is then labeled, and the level of the solution is marked. As soon as the patient is brought into the operating room, the intravenous infusion is begun at a fairly rapid rate (about 100 drops per minute). It is planned that the patient will receive about 100 cc. of the solution while being prepared for the operation. By observing him closely, one can see him relax; as soon as his replies are subdued, the rate of flow is decreased, but in most cases a slow drip is maintained throughout the operation. A resident physician is charged with observing the flow of this hypnotic and notes the total amount used at the end of the operation. The same bottle is used in subsequent cases, but the needle and plastic tubing are changed between operations. The only premedication on the day of the operation is meperidine hydrochloride, 50 to 100 mg., given by hypodermic injection 45 minutes before operation. On the night before the operation, pentobarbital sodium, 1½ grains is given by mouth.

Results of Intravenous Method of Sedation with Pentobarbital in Seventy-Five of Eighty Cases of Operation on the Eye

	Successful	Unsuccessful
Cataract extraction	47	1
Cyclodiathermy	6	2
Retinal reattachment	5	..
Iridectomy	4	..
Muscle operations	2	2
Excision of pterygium	4	..
Enucleation	3	..
Plastic operation	2	..
Needling	1	..
Removal of intraocular foreign body	1	..
Total	75	5

Results.—The sedation obtained by this method was successful in 75 of 80 cases. A successful result meant that the patient was relaxed or asleep during the operation and that he did not complain. Many patients experienced amnesia, and some of them had to be convinced that the operation had already been completed. The result was declared unsuccessful if the patient was uncooperative and complaining; in brief, such a patient should, preferably, have had a general anesthetic.

The amount of pentobarbital used varied from ½ to 5 grains (0.03 to 0.3 gm.), the average being 1.9 grains (0.124 gm.). There were six cases of postoperative nausea and vomiting in this series. In three cases of cataract nausea and vomiting occurred postoperatively, and in one vomiting was preoperative. In one case of muscle operation these complaints preceded and followed surgery, and in one case of detached retina, they occurred postoperatively.

The routine use of dimenhydrinate (Dramamine) would, no doubt, diminish the number of cases of nausea and vomiting; it was, indeed, used in two cases. In one of them vomiting occurred before the operation, no doubt because of the meperidine, and was stopped by the use of dimenhydrinate. In another nausea was expected, and was prevented through its use. However, the routine use of this drug was purposely omitted in the present series.

Advantages.—The method described offers the following advantages: 1. The dose of the barbiturate can be accurately controlled. 2. The barbiturate is given at a time when it is needed most. This is of especial importance, since in a heavily scheduled operating room one cannot always predict the time at which the operation will take place. 3. Full relaxation is obtained, and the patient usually drifts into a sleep which is beneficial, not only to him but also to the surgeon. 3. Nothing has to be given by mouth before operation, and the absence of a bitter barbiturate in the stomach should reduce nausea and vomiting. Finally, a certain degree of amnesia often results.

Disadvantages.—The main disadvantage of this method is that a person must be available in the operating room to regulate the flow of the hypnotic according to the surgeon's directions. Although the solution is very dilute, the danger of overdosage is nevertheless to be kept in mind, for reasons that are obvious. The preparation of the solution and the difficulty that is sometimes met in finding a vein also require more of the surgeon's time.

SUMMARY

Controlled and satisfactory sedation during eye surgery was attained in 75 of 80 cases in which a continuous drip of dilute pentobarbital (Nembutal) sodium was administered intravenously just before and during the operation. The average dose of the barbiturate needed was only slightly less than 2 grains; the only premedication was the subcutaneous injection of 50 to 100 mg. of meperidine (Demerol) hydrochloride. Routine local anesthesia was used in and about the eye.

It is often possible to proceed with surgery with this type of sedation when otherwise a general anesthetic would have been required.

727 W. 7th St. (17).

ASPIRATION OF THE LACRIMAL SAC IN ACUTE DACRYOCYSTITIS

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IN A RECENT publication, the use of penicillin in the lacrimal sac for the treatment of acute dacryocystitis was reported.[1] It was surprising to note that the penicillin was introduced into the sac by means of a No. 20 hypodermic needle entered through the skin over the sac, after anesthetizing it with an injection of procaine hydrochloride. The introduction of the antibiotic into the sac can usually be accomplished by means of a curved lacrimal cannula introduced through the lower canaliculus without puncturing the skin, and with relatively little discomfort.

It does take longer to anesthetize the punctum and canaliculus when the tissues are acutely inflamed, but with care it can be accomplished.

A cocaine or tetracaine-soaked pledget sufficiently large to fill the medial canthus and cover the lower punctum thoroughly is left in contact for five minutes, and this procedure is repeated three times for the same length of time. The cannula is then placed over the punctum opening, and cocaine or tetracaine is injected into the canaliculus after the application of each pledget. The punctum can then be gently dilated sufficiently to admit the curved cannula, loosely attached to a 2 cc. syringe with a small amount of tetracaine in it. This curved cannula can usually be passed gently into the sac and pus aspirated from the sac. The cannula is left in place and the syringe replaced with another, containing 0.25 to 0.5 cc. of 4% cocaine hydrochloride or 1% tetracaine hydrochloride, which is gently introduced into the sac.

This syringe is then removed and replaced with another, containing either penicillin or 30% sulfacetimide, with which the sac may be flushed gently, and then some clean solution may be left in the sac. I have found either solution to work well. Care must be taken not to injure the lacrimal canaliculus.

It will occasionally be found that the entrance of the canaliculus to the sac is densely obstructed, in which case the technique described by the Cusicks is indicated. This consists of anesthetizing the skin over the sac with procaine and then introducing a No. 20 needle through the skin into the sac, aspirating the pus, and introducing the antibiotic into the sac.

I have found the technique described here equally useful in acute and in chronic dacryocystitis when the patient is old enough to cooperate for local anesthesia. In young persons a few whiffs of vinyl ether (Vinethene) suffices for introduction of the cannula, aspiration, and irrigation of the sac. One treatment will often get the patient over the acute attack, so that the obstruction to the nasolacrimal duct may be taken care of by a dacryocystorhinostomy.

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1. Cusick, P. L., and Michael, M. J.: Penicillin in Dacryocystitis, Kresge Eye Inst. Bull. **3**:62 (Feb.) 1952.

Registry of Interesting Cases

It is the purpose of this section to record cases on the basis of interest only. No complete review of the literature is attempted and no claim for priority is implied except when specifically stated. Publication of case reports is subject to the concurrence of the Editorial Board on the interesting aspects of the case. It is requested that the reports submitted be as brief as is consistant with inclusion of the pertinent facts, bear a title that is as specific as possible, be prefaced by a paragraph that states why the author feels the case is of interest and be accompanied with photographs whenever possible.

TRANSIENT GLAUCOMA ASSOCIATED WITH MENINGEAL HYDROPS

THE SYNDROME of meningeal hydrops is known to present considerable variation in symptoms and signs, and these have been recorded in detail in the literature. However, the association of transient glaucoma and meningeal hydrops has not to my knowledge been described. Because the ophthalmologist frequently participates in the diagnosis and observation of this condition, a case in which glaucoma occurred during the acute phase of meningeal hydrops may be of interest.

REPORT OF CASE [1]

History.—R. A., a white man aged 34, an office worker, was admitted to the Albany Hospital on June 18, 1952, to the service of Dr. William B. Scharfman and Dr. Simon Propp. There was nothing of note in the history except that the patient had been on a reducing diet since January, 1952, and had lost about 30 lb. (13.6 kg.). He had been in good general health until about two weeks before admission, when he noticed a feeling of malaise. His temperature was found to be 104 F., with fluctuations to 99 F. during the next few days. He was given two injections of penicillin by his family physician. A generalized rash followed the second injection.

About 10 days before admission he began to complain of severe, constant bifrontal headache. This persisted up to the time of his admission, and during the six days before coming to the hospital he experienced persistent nausea and occasional vomiting.

On June 20, shortly after entering the hospital, the patient for the first time noted halos around the light bulbs in his room and slight blurring of vision. There was no pain in the eyes and no diplopia. About this time he observed that his eyes were a trifle "bloodshot"; there was no discharge from the eyes.

Clinical Examination.—I saw the patient on June 21. At this time vision without correction was 20/15 in each eye; however, he still complained that objects appeared slightly blurred. There were a slight, but definite, pericorneal blush and mild bedewing of the corneal epithelium. The pupils were equal in size, and their reactions were normal. The two irises were the same shade of blue. The anterior chamber was of average depth, and the angle was not shallow. Slit-lamp examination revealed no flare, cells or keratic precipitates. On the posterior portion of each iris at the pupillary margin were a few tiny, pale blisters, suggestive of Koeppe nodules.

The vitreous appeared to be clear in both eyes. The fundi could be seen without difficulty, although there was a slight haze, due to the corneal edema. The disk edges were not sharply defined, but no elevation of the disks was observed and the veins did not appear abnormal; there was a spontaneous venous pulse on each disk. There were no hemorrhages or signs of edema around the disks. It was felt that disks of this type were seen normally in some patients; however, it was noted that such disks are sometimes seen in the very earliest stage of papilledema.

The ocular tension was 45 mm. Hg (Schiøtz) in the right eye and 50 mm. in the left eye.

1. Drs. Eldridge Campbell, Simon Propp, and William B. Scharfman gave me permission to report this case.

Course.—The patient was placed on a fairly intensive schedule of instillations of 4% pilocarpine nitrate drops in each eye, and the next day the tension was 15 mm. Hg. The halos had completely disappeared, and the slight residual blurring of vision was thought to be due to the frequent use of drops. The pupil was well contracted. The bulbar conjunctiva seemed to be more injected than before the use of the drops. Slit-lamp examination again revealed the absence of signs of iridocyclitis. The previously noted blisters on the edge of the iris were again noted.

Examination of the peripheral fields (3/330 white target) showed a normal condition for each eye. As examination of the central field was begun, the patient noted severe malaise, lightheadedness, and perspiration. He felt so ill that he was unable to go through with the rest of the test.

After a few days the pilocarpine drops were reduced in strength and frequency of instillation, and normal tension was easily maintained. While the ocular complaints were relieved, the severe, constant headache, nausea and vomiting, as well as low-grade fever, persisted.

On June 23, lumbar puncture revealed a spinal fluid pressure of 360 mm. of water, with swings to 420 mm. The fluid was clear and colorless. The total protein content was 70 mg. per 100 cc., with 31 lymphocytes per cubic millimeter.

The fundi had not been visible since the instillation of pilocarpine drops was started. In view of the increased spinal fluid pressure, another examination of the fundi seemed advisable. Therefore use of the pilocarpine was discontinued on June 23, and the next day the fundi were reexamined. The disks had changed considerably from the equivocal appearance noted on my first examination. In order that I might check the condition of the fundi more carefully, on June 25 the pupils were widely dilated with 10% phenylephrine (Neosynephrine) hydrochloride. There was no posterior synechia or other gross evidence of iridocyclitis. The tension remained normal. (Because of continued severe headaches, nausea, and malaise, the patient was confined to bed from June 22 on, and no further slit-lamp examinations could be performed.) The fundi were then well visualized through dilated pupils and clear media. Striking changes in the disks were then observed. There was typical, well-established papilledema in each eye, slightly more pronounced in the right. The right disk was elevated 1.5 to 2.0 D., and there were several peripapillary flame-shaped hemorrhages. The left disk was elevated about 1.0 D., and no hemorrhages were seen around it.

A ventriculogram, performed by Dr. Eldridge Campbell on June 25, resulted in good delineation of the lateral and third ventricles; there was no evidence of any displacement, deformity, or dilatation.

The pilocarpine drops were discontinued June 25, and the ocular tension varied from 14 to 22 mm. Hg during the rest of his hospital stay.

On June 25 administration of aureomycin, 250 mg. every three hours, was begun. The temperature gradually fell to a normal level and remained so from June 27 on.

Lumbar punctures were repeated several times, with the following results.

	Mm. Water
6/29	480
6/30	360
7/ 1	490
7/ 5	600
7/ 9	490
7/17	370

Frequent examination of the fundi showed that the papilledema persisted, with the addition of numerous superficial hemorrhages around both disks, particularly on the right side.

The general complaints of headache, nausea, and malaise progressively cleared. Despite the dramatic appearance of the fundi, vision remained perfectly clear. The patient occasionally noted momentary diplopia a few times a day; however, this gradually disappeared during the next few weeks.

The patient was discharged free from ocular and general complaints on July 18. The papilledema at this time had not receded significantly. The visual acuity and visual fields prior to discharge were essentially normal except for the enlarged blind spots, due to the papilledema. The spinal fluid pressure at the time of discharge was still elevated (370 mm.).

The patient was seen once every week or two in my office. At no time did he experience any transient black-outs of vision or other danger signs indicating poor tolerance of the papilledema. Vision remained normal, and the fields were not abnormal except for a fairly consistent relative constriction in the right inferior nasal area. The blind spots gradually decreased in size, along with the subsidence of the papilledema. The ocular tension remained normal without use of drops. The small blisters on the pupillary margin had disappeared.

On Sept. 13, examination of the fundi revealed striking improvement; all the hemorrhages had absorbed, and there was no measurable elevation of either disk; however, the edges of the disks were not sharply outlined.

The patient was last examined on Jan. 6, 1953, at which time he was free from complaints.

Laboratory Data.—The urine was normal except for a 2+ reaction for albumin on June 19, 1952; findings on later examinations were entirely normal. The serologic reactions were negative. The white blood cell count was 10,650, with 82% segmented forms. A roentgenogram of the chest revealed nothing abnormal. The spinal fluid protein was 70 mg. per 100 cc., with 31 lymphocytes per cubic millimeter. Serum protein was 7.6 gm. per 100 cc. The albumin-globin ratio was reversed. Typhoid, brucellosis, tularemia, and heterophile agglutination tests gave negative results. Examination of the ventricular fluid showed 70 mg. of protein, 110 mg. of sugar, and 124 mg. of chloride, per 100 cc. A smear of ventricular fluid revealed Gram-positive bacilli, and the culture yielded Bacillus subtilis.

Comment.—The nature of this episode of glaucoma is not entirely clear. On first discovery of the elevation in tension, it seemed conceivable that, in the absence of more definite evidence of iridocylitis, an ordinary, wide-angle glaucoma might have been brought into the open by the stresses associated with a severe systemic illness. However, in view of the appearance of this glaucoma during the acute phase of the meningeal hydrops and its subsidence with improvement in the patient's general condition, it seems more likely that the glaucoma was somehow associated with and related to the systemic disease. It should be noted that there was a period of about two weeks during which the patient's general condition was such that complete bed rest became essential and slit-lamp examination could not be performed. It is possible that additional signs of iridocyclitis, not visible on bedside examination, went undetected during that interval.

Worthy of mention are the striking changes in the disks, from a borderline normal condition, at the time of elevated ocular tension, found on the first examination, to full-blown papilledema, a few days after normalization of the ocular tension. It is interesting to speculate whether the increased tension was enough to hold back and suppress the papilledema, which appeared shortly after the ocular tension was normalized.

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Annual Reviews

PHARMACOLOGY AND TOXICOLOGY

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THIS paper constitutes a review of the literature from the spring of 1952 to the spring of 1953 as it pertains to the physiologic response to certain drugs which the ophthalmologist finds of value. The large volume of literature, particularly on such topics as the antibiotics and cortisone, has made impossible the compilation of an all-inclusive bibliography. In order that continuity of subject matter may be maintained, material which has been published in previous years is alluded to but is not listed in the bibliographic references.

CHEMOTHERAPEUTIC AGENTS [1]

ANTIBIOTICS AND SULFONAMIDES

Mode of Action.—During the year under review little new has been added to our knowledge of the mode of action of the sulfonamides. The time-honored theory holds that these drugs inhibit bacterial utilization of *p*-aminobenzoic acid, since this compound can overcome the antimicrobial action of the sulfonamides. These two compounds are chemically similar. The sulfonamide drugs presumably "saturate" the enzyme system which is responsible for the metabolism of *p*-aminobenzoic acid and thus prevent the latter from fulfilling its normal function. (The "lock-and-key" concept of competitive action is, of course, not new and finds wide application in the field of pharmacology.) This theory of action of these agents is still generally accepted, although the possibility of inhibition of other enzyme systems must be credited. In this connection, the poisoning of carbonic anhydrase by sulfonamides is interesting. Certain derivatives of sulfanilamide are particularly potent carbonic-anhydrase inhibitors and, by virtue of this action, have a pronounced effect on gastric secretions and kidney tubule function in the human.[2]

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1. A chemotherapeutic agent is considered to be a drug used in the treatment of infection (Marshall, E. K.: The Dosage Schedule of Chemotherapeutic Agents, Pharmacol. Rev. **4**:85-105, 1952).

2. Birnbaum, D., and Hollander, F.: Inhibition of Pancreatic Secretion by the Carbonic Anhydrase Inhibitor, 2-Acetylamino-1,3,4-Thiadiazole-5-Sulfonamide (Compound #6063), Proc. Soc. Exper. Biol. & Med. **81**:23, 1952. Janowitz, H. D.; Colcher, H., and Hollander, F.: Carbonic Anhydrase Inhibition and Gastric Secretion, Tr. New York Acad. Sc. **15**:54, 1952. Maren, T. H.: Pharmacological and Renal Effects of Diamox (6063) a New Carbonic Anhydrase Inhibitor, ibid. **15**:53, 1952. McGowan, J. A.; Stanley, M. M., and Powell, J. J.: Effect of 2-Acetylamino-1,3,4-Thiadiazole-5-Sulfonamide (6063: Diamox) on the Secretion of Gastric Hydrochloric Acid in Man, Bull. New England M. Center **14**:117-121, 1952.

The mode of action of various antibiotics has recently been reviewed.[3] Certain antibiotics may have surface activity and act by increasing the permeability of the bacterial membrane.[4] However, the majority of antibiotics undoubtedly are antibacterial because of their ability to interfere in some way with the metabolic function essential to the life or growth of the microbe.[5] Among the various effects attributed to these drugs are decreased protein synthesis, impaired utilization of certain amino acids, such as phenylalanine, and inhibition of prosphorylation. The list is not complete. Indeed, a unified concept is not possible at present. The specific function or functions which are affected vary with the antibiotic, and probably with the organism, so that a given antibiotic may affect different enzyme systems in various bacteria. As would be expected, the in vitro activity of the various antibiotics can be shown to vary with the pH and the composition of artificial media.[6]

If the antibiotics exert their effect by interfering with the metabolism of the bacterial cell while leaving the host cell unaltered, it would be illogical to expect an activity against viruses, since these infectious agents appear to have no intrinsic metabolic activity.[7] The exact boundary of viruses is ill-defined, however, and some antibiotics do appear to alter the course of some experimental and clinical viral diseases, notably those due to the larger viruses of the psittacosis group (Chlamydozoaceae). The pleuropneumonia and Rickettsial organisms, which probably represent the next higher order in biochemical complexity, are inhibited by certain of the antibiotics.

Some antibiotics (oxytetracycline [Terramycin], chloramphenicol, and aureomycin) are considered to be bacteriostatic only. Others (penicillin and streptomycin) are bactericidal as well. A new antibiotic, erythromycin, falls in the latter group.[8] In any event, the antibiotics exert their most potent effect against a bacterial colony which is in an active growth (logarithmic) phase, rather than in a stationary

3. Wyss, O.; Smith, G. N.; Hobby, G. L.; Oginsky, E. L., and Pratt, R.: Symposium on the Mode of Action of Antibiotics, Bact. Rev. **17**:17-49, 1953.

4. Sacks, L. E.: Subtilin Considered as a Germicidal Surface-Active Agent, Antibiotics & Chemother. **2**:79-85, 1952. Tolstoouhov, A. V.: Physical-Chemical Approach to the Problems of Chemotherapy, Tr. New York Acad. Sc. **14**:260, 1952.

5. Bergmann, E. D., and Sicher, S.: Mode of Action of Chloramphenicol, Nature, London **170**:931-932, 1952. Bernheim, F., and De Turk, W. E.: Effect of Chloramphenicol and Certain Other Drugs on the Oxidation of Aromatic Amino Acids by a Strain of Pseudomonas Aeruginosa, J. Pharmacol. & Exper. Therap. **105**:246, 1952. Long, P. H.: Mode of Action of Antibiotics, New York J. Med. **52**:1637-1639, 1952. Miura, Y.; Nakamura, Y.; Matsudaira, H., and Komeiji, T.: Mode of Action of Terramycin, Antibiotics & Chemother. **2**:152-158, 1952. Umbreit, W. W., and Oginsky, E. L.: Mode of Action of Antibiotics: Penicillin and Streptomycin, J. Mt. Sinai Hosp. **19**:175, 1952. Van Meter, J. C.; Spector, A.; Oleson, J. J., and Williams, J. H.: In Vitro Action of Aureomycin on Oxidative Phosphorylation in Animal Tissues, Proc. Soc. Exper. Biol. & Med. **81**:215, 1952.

6. Eagle, H.; Levy, M., and Fleishman, R.: Effect of the pH of the Medium on the Antibacterial Action of Penicillin, Streptomycin, Chloramphenicol, Terramycin, and Bacitracin, Antibiotics & Chemother. **2**:563-575, 1952. Weinberg, E. D.: Influence of Various Sources of Nitrogen on the Activity of Antibiotics, ibid. **2**:130-134, 1952.

7. Levaditi, C.: Pour quelles raisons les antibiotiques n'agissent-ils pas sur les ultravirus? Presse méd. **60**:133-134, 1952.

8. Haight, T. H., and Finland, M.: Observations on Mode of Action of Erythromycin, Proc. Soc. Exper. Biol. & Med. **81**:188, 1952.

(plateau) phase, the reason being that the metabolic activity is more intense in the logarithmic phase. The significance of this fact in the treatment of disease has been well demonstrated in experimental infections. Eradication of an infectious process is much more readily achieved where an increasing bacterial population, rather than a stationary one, is involved.[9] This observation bears out clinical experience. Some antibiotics, e. g., neomycin, may be very effective against bacteria in the stationary phase.[10]

As a group, the antibiotics vary widely in their chemistry. Some, such as the polymyxins [11] and bacitracin, contain polypeptide linkages, whereas others are cyclic or heterocyclic compounds. Oxytetracycline and aureomycin have been found to be very similar chemically.[12] This undoubtedly accounts for their similarity in bacterial spectrums and side-reactions and for the cross resistance between the two that is observed clinically. Many studies have been made to determine the specific grouping which confers on a given antibiotic its antibacterial action.[13] No one particular grouping in any of the antibiotics can be cited as that solely responsible for its activity.

One of the intriguing properties of the antibiotics, notably aureomycin, is their ability to stimulate growth. Particularly in combination with vitamin B_{12}, they have been found to accelerate the weight gain of certain experimental and domestic animals and fowls.[14] The exact role which the antibiotics play in stimulating growth is not established. The combined use of aureomycin and vitamin B_{12} counteracts to a large extent the growth inhibition which cortisone induces experimentally.[15] Antibiotics have also been reported to stimulate plant growth.[16]

9. Eagle, H.: Experimental Approach to the Problem of Treatment Failure with Penicillin: I. Group A Streptococcal Infection in Mice, Am. J. Med. **13**:389-399, 1952.

10. Schoenhard, D. E., and Stafseth, H. J.: Some Observations on the in Vitro Action of Neomycin, Antibiotics & Chemother. **2**:41-50, 1953.

11. Brownlee, G.; Bushby, S. R. M., and Short, E. I.: Chemotherapy and Pharmacology of the Polymyxins, Brit. J. Pharmacol. **7**:170-188, 1952.

12. Dunitz, J. D., and Robertson, J. H.: Relationship Between Aureomycin and Terramycin, J. Am. Chem. Soc. **74**:1108, 1952. Pepinsky, R., and Watanabe, T.: Isomorphism of Terramycin and Aureomycin Hydrochlorides, Science **115**:541-543, 1952. Regna, P. P.: Chemical Structure of Terramycin in Relation to Mode of Action, Tr. New York Acad. Sc. **15**:12, 1952.

13. Collins, R. J.; Ellis, B.; Hansen, S. B.; Mackenzie, H. S.; Moualim, R. J.; Petrow, V.; Stephenson, O., and Sturgeon, B.: Some Observations on the Structural Requirements for Antibiotic Activity in the Chloramphenicol Series: II. J. Pharm. & Pharmacol. **4**:693-710, 1952. Umbreit, W. W.: Symposium on Chemical Structure of Antibiotics in Relation to Mode of Action: Streptomycin, Tr. New York Acad. Sc. **15**:8-12, 1952.

14. Arnrich, L.; Lewis, E. M., and Morgan, A. F.: Growth of Dogs on Purified Diet Plus Aureomycin and/or Vitamin B_{12}, Proc. Soc. Exper. Biol. & Med. **80**:401-404, 1952. Brown, P. B.; Becker, D. E.; Terrill, S. W., and Card, L. E.: Effect of Aureomycin on the Growth and Metabolism of the Pig, Arch. Biochem. **41**:378-382, 1952. Cuthbertson, W. F. J.: Nutritional Significance of the Animal Protein Factor and Antibiotics, Brit. J. Nutrition **6**:330-335, 1952. Lawrence, J. M., and McGinnis, J.: Effect of Terramycin on the Growth of Rabbits, Arch. Biochem. **37**:164-166, 1952. Weber, E. M.; Luther, H. G., and Reynolds, W. M.: Antibiotics as Animal-Growth Stimulants, Bull. World Health Organ. **6**:149-161, 1952.

15. Meites, J.: Beneficial Effects of Vitamin B_{12} and Aureomycin in Rats Given Large Doses of Cortisone, Proc. Soc. Exper. Biol. & Med. **81**:307, 1952.

16. Nickell, L. G.: Stimulation of Plant Growth by Antibiotics, Proc. Soc. Exper. Biol. & Med. **80**:615-617, 1952.

A protective effect of antibiotics against lethal doses of x-radiation has been reported in the rat and dog.[17] This effect appears to be due simply to control of the infectious process.

Bacterial Resistance.—In many respects this is a corollary of the preceding topic and can be considered to have several facets. First, some bacteria simply are, and were from the start, insensitive to certain antibiotics. Second, over a period of years an increasing number of resistant strains have emerged from among bacteria which at one time were extremely sensitive to antibiotics. This is particularly true of staphylococci.[18] The number of strains of staphylococci resistant to penicillin and the sulfonamides has increased considerably in the last several years. A typical report from one laboratory showed that the percentage of strains of Staphylococcus aureus resistant to penicillin increased from 16%, in 1948-1949, to 59%, in the period from 1949 to 1951. Resistance of the same organisms to sulfonamides increased from 22% to 72% during the same period. Moreover, an increasing incidence of resistance of the staphylococci to the broad-spectrum antibiotics is reported. The increase in resistant strains appears to be more a property of the organism than of the antibiotic or its improper use, since the sensitivity of Treponema pallidum to penicillin has not been altered appreciably over a period of years.

The third facet concerns the development of bacterial resistance during therapy with antibiotics. Clinically, this has been no great problem except with the use of streptomycin, although acquired resistance to most antibiotics can be demonstrated experimentally in vivo and in vitro. Of the many possible explanations for the development of an acquired resistance, those that receive the most support are (*a*) the selective growth of an originally resistant cell; (*b*) the cytoplasmic adaptation to the agent by the cell, which may simply tolerate the drug, actively destroy it, or become dependent on the antibiotic, and (*c*) chromosomal adaptation, with the emergence of a resistant mutant.[19] In general, development by an organism of resistance to one antibiotic does not affect its sensitivity to others, except that cross resistance may develop among aureomycin, oxytetracycline, and chloramphenicol, particularly the first two.[20]

17. Furth, F. W.: Coulter, M. P., and Howland, J. W.: Effect of Aureomycin on the Radiation Syndrome in Dogs, Am. J. Path. **28**:25-36, 1952; Effect of Aureomycin and Terramycin on the X-Radiated Rat, ibid. **28**:185-191, 1952. Kaplan, H. S.; Speck, R. S., and Jawetz, E.: Impairment of Antimicrobial Defenses Following Total Body Irradiation of Mice, J. Lab. & Clin. Med. **40**:682, 1952.

18. Birnstingl, M. A.: Shooter, R. A., and Hunt, M. G.: Sensitivity to 5 Antibiotics of Strains of Staph. Pyogenes Isolated from Out-Patients, Brit. M. J. **1**:253-254, 1952. Koch, M. L., and Bourgeois, R. W.: Report on a Further Increase in the Incidence of Drug-Resistant Pathogenic Staphylococci Encountered in the Hospital Laboratory, Antibiotics & Chemother. **2**:229-233, 1952. Lund, E.: Determination of the Sensitivity of Bacteria to Aureomycin, Chloromycetin, and Terramycin, Acta path. et microbiol. scandinav. **31**:281-288, 1952. Wilson, R., and Cockcroft, W. H.: Penicillin Resistant Staphylococcal Infection, Canad. M. A. J. **66**:548-551, 1952.

19. Cavalli, L. L.: Genetic Analysis of Drug-Resistance, Bull. World Health Organ. **6**:185-206, 1952. Sevag, M. G., and Rosanoff, E. I.: Mechanism of the Development of Resistance to Streptomycin: I. Origin of Resistant Strains, J. Bact. **63**:243-251, 1952. Welsch, M.: Some Aspects of Microbial Resistance to Streptomycin, Bull. World Health Organ. **6**:173-183, 1952.

20. Fusillo, M. H.; Romansky, M. J., and Kuhns, D. M.: Further Investigations on Cross Resistance as Well as Studies on Induced Sensitivity to the Antibiotics, Antibiotics & Chemother. **3**:35-41, 1953.

Absorption and Tissue Penetrability.—With the exception of streptomycin, which is not absorbed from the gastrointestinal tract, the antibiotics commonly used systemically are available in palatable oral form.[21] Oral administration of penicillin appears to be quite as effective as parenteral,[22] although a higher dose (1,000,000 to 1,500,000 units a day) is required. The possibility that oral administration may reduce hypersensitivity reactions to penicillin has led some to prefer this route. N,N'-dibenzylethylenediamine penicillin is a highly insoluble salt, valuable as a long-acting repository penicillin and palatable in suspension form because of its insolubility. Combined administration of penicillin and certain agents which interfere with the excretion of the antibiotic by the kidney tubules results in higher antibiotic levels in the blood. The compound which seems to give best results in this respect is probenecid (Benemid),[23] in divided doses of 2 to 3 gm. daily. (Probenecid also promotes the excretion of uric acid and is of value, therefore, in the treatment of gout.) Chloramphenicol (Chloromycetin) palmitate is a synthetic ester of chloramphenicol which is palatable in suspension.[24] The ester has no antibiotic action but is readily hydrolyzed to the active antibiotic. The two newer antibiotics, erythromycin and magnamycin, are absorbed from the gastrointestinal tract.[25] A higher blood level of erythromycin is obtained when it is administered as enteric-coated tablets, rather than as the usual tablet form. Aureomycin and oxytetracycline are poorly absorbed from the rectum,[26] and the rectal route of administration is not recommended.

It is reasonable to assume that the antibiotics and sulfonamides distribute themselves equally in the extracellular water. As might be expected, however, they enter the cerebrospinal fluid and aqueous humor poorly. This is true of the newer antibiotics (erythromycin) as well.[27] Of these agents, certain of the sulfonamides and

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21. Woodard, W. A.: Recent Developments in the Pharmacy of Antibiotics, J. Pharm. & Pharmacol. **4**:1009, 1952.

22. Fisher, A. M.: A Trial of Oral Penicillin, New Zealand M. J. **51**:418-419, 1952. Lepper, M. H.; Rodriguez, J.; Blatt, N., and Spies, H. W.: Use of Dibenzylethylenediamine Penicillin Administered Orally in Bacterial Infections, Antibiotics & Chemother. **2**:175-178, 1952.

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25. Finn, J. J., and Kane, L. W.: Magnamycin, a New Antibiotic, Bull. New England M. Center **14**:113, 1952. Josselyn, L. E., and Sylvester, J. C.: Absorption of Erythromycin, Antibiotics & Chemother. **3**:63-67, 1953.

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chloramphenicol penetrate the blood-aqueous and blood-cerebrospinal fluid barriers most readily, although concentrations equal to those in the plasma are never achieved in these fluids. Of particular interest is a newer preparation, the diethylaminoethyl ester of benzyl penicillin (penicillin G), which, as the hydriodide salt, is marketed as Neo-penil.[28] This ester is absorbed poorly from the gastrointestinal tract and, as a repository penicillin, gives somewhat lower blood levels than procaine penicillin. However, it is readily concentrated by certain tissues, such as the lung, and is found in high concentrations in the sputum. Moreover, its concentration in the cerebrospinal fluid reaches levels approximately 10 times as great as can be produced by equivalent doses of penicillin in other forms. By inference, the concentration in the eye should be equally high. Since the ester itself is antibiotically inactive, the question has been raised whether these high concentrations represent any additional therapeutic benefit.[29]

The intraocular penetration of these agents through the intact cornea is limited, and local application should not be relied upon for intraocular therapy. On the other hand, penetration from subconjunctival injection may be comparatively good,[30] and this route of administration is recommended for various ocular and intraocular infections. In treating the latter, systemic administration is also necessary.

Hazards of Administration of Antibiotics and Sulfonamide Drugs.—An excellent review of this subject has been recently published.[31] In general, there are two types of hazards. The first is the emergence of infections due to organisms insensitive to the usual antibiotics, notably the resistant staphylococci, Proteus vulgaris, Pseudo-

28. Flippin, H. F.; Matteucci, W. V.; Schimmel, N. H.; Bartholomew, L. E., and Boger, W. P.: The Hydriodide of Diethylaminoethyl Ester of Penicillin G, Neo-Penil, Antibiotics & Chemother. **2**:208-214, 1952. Flippin, H. F.; Unangst, W. W.; Schimmel, N. H.; Bartholomew, L. E., and Matteucci, W. V.: The Hydriodide of Diethylaminoethyl Ester of Penicillin G, Neo-Penil: II. J. Philadelphia Gen. Hosp. **3**:57-60, 1952. Grigsby, M. E.; Haight, T. H., and Finland, M.: Some Clinical and Laboratory Observations on the Hydriodide of Diethylaminoethyl Ester of Penicillin G (Neo-Penil), New England J. Med. **247**:807-811, 1952. McDonald, G. L., and Thomson, E. F.: Penicillin Levels in the Sputum Following Intramuscular Injections of "Estopen," M. J. Australia **2**:407-408, 1952. Nielson, A. T., and Roholt, K.: A Note on Benzylpenicillin Diethylaminoethyl Ester, J. Pharm. & Pharmacol. **4**:266-267, 1952. Rhodes, R. E.; Parmelee, E. T., and Ferlauto, R. J.: β-Diethylaminoethyl Ester of Benzyl Penicillin: I. A Preliminary Report on Tissue Compounds, Antibiotics & Chemother. **2**:389-393, 1952. Schimmel, N. H.; Wilson, W. W.; Matteucci, W. V., and Flippin, H. F.: The Hydriodide of Diethylaminoethylester Penicillin-G, Neo-Penil: III. Unusually High Penicillin Concentrations in Cerebrospinal Fluid Following Intramuscular Administration, Am. J. M. Sc. **224**:247-251, 1952.

29. Hallas-Moller, K.; Juncher, H. O.; Moller, C., and Wille, B.: Chemical and Biological Investigations of an Organ-Specific Derivative of Penicillin: The Hydriodide of the Benzyl Penicillin—Diethyl—Aminothanol Ester, Antibiotics & Chemother. **2**:334-343, 1952.

30. (*a*) Cannon, E. J.; Nichols, A. C., and Leopold, I. H.: Studies on the Intraocular Penetration and Toxicity of Terramycin, A. M. A. Arch. Ophth. **47**:344-349, 1952. (*b*) Ainslie, D., and Smith, C.: Polymyxin E Penetration into the Eye and Therapeutic Value of Experimental Infection Due to Ps. Pyocyanea, Brit. J. Ophth. **36**:352-361, 1952. (*c*) Sorsby, A.; Ungar, J., and Bailey, N. L.: Streptomycin in Ophthalmology, Brit. M. J. **1**:119-123, 1952.

31. Finland, M. F., and Weinstein, L.: Complications Induced by Antimicrobial Agents, New England J. Med. **248**:220-226, 1953.

monas aeruginosa, and Candida albicans.[32] It is interesting to note that the simultaneous injection of aureomycin and C. albicans into mice may be fatal, whereas the injection of either one alone results in no ill effect.[33] Serious ocular infections with P. vulgaris and Ps. aeruginosa are being reported with increasing frequency. The usual history of the emergence of resistant infections is one of an infectious process which initially subsides under antibiotic therapy only to blossom out again. Treatment of these resistant strains may be difficult. The antibiotic in use must be discontinued and the problem reevaluated. Sensitivity tests, of course, are essential.

The other hazards of antibiotic therapy concern the effect of the antibiotic itself on the patient under treatment. One of these untoward responses is the hypersensitivity reaction. The skin is the organ most frequently involved, and the antibiotic oftenest incriminated is penicillin. This drug may cause a variety of dermatologic manifestations.[34] Streptomycin and the sulfonamides are also notorious for their allergenic properties.[35] Sensitization may result from local application to the skin and conjunctiva. The importance of distinguishing between drug sensitivity and drug irritation of the conjunctiva has been emphasized.[36] Other untoward effects due to a hypersensitive state may occur, particularly with the use of penicillin. These include a serum-sickness-like response[37] and an anaphylactic reaction, which may be fatal.[38] The therapeutic use of antihistaminics has certain rationale and

32. McCurdy, R. S., and Neter, E.: Effects of Penicillin and Broad-Spectrum Antibiotics on Emergence of a Gram-Negative Bacillary Flora in the Upper Respiratory Tract of Infants, Pediatrics **9**:572-576, 1952. McGovern, J. J.; Parrot, R. H.; Emmons, C. W.; Ross, S.; Burke, F. G., and Rice, E. C.: Effect of Aureomycin and Chloramphenicol on the Fungal and Bacterial Flora of Children, New England J. Med. **248**:397-403, 1953. Yow, E. M.: Development of Proteus and Pseudomonas Infections During Antibiotic Therapy, J. A. M. A. **149**:1184-1187, 1952.

33. Seligmann, E.: Virulence-Enhancing Activities of Aureomycin on Candida Albicans, Proc. Soc. Exper. Biol. & Med. **79**:481-484, 1952.

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35. Evans, F., and Gould, J.: Relation Between Sensitivity to Thiopentone, Sulphonamides, and Sulphathiazole, Brit. M. J. **1**:417-419, 1952. Ghosh, M. N.: Fixed Eruption Due to Sulphonamide Hypersensitivity, ibid. **2**:26, 1952. Jeffrey, B.; Borrie, P., and MacDonald, N.: Acquired Hypersensitivity to Sodium PAS, Streptomycin, and Penicillin, ibid. **2**:647-649, 1952. Kooij, R., and van Vloten, T. J.: Epidermal Sensitization Due to Sulphonamide Drugs: Groups- and Cross-Sensitivity; Photosensitivity; Passive Transfer of Antibodies; Leftwich Reaction, Dermatologica **104**:151-167, 1952. Seeberg, G.: Demonstration of Antibodies in Streptomycin Eczema by the Collodion Agglutination Test, Acta dermat.-venereol. **32**:355-363, 1952.

36. Theodore, F. H.: Drug Sensitivities and Irritations of the Conjunctiva, J. A. M. A. **151**:25-30, 1953.

37. Riley, K. A.: Serum Sickness from Penicillin: A Report of 22 Cases, A. M. A. Arch. Dermat. & Syph. **65**:727, 1952.

38. Christenson, W. N.; Hedrick, G. W., and Schugmann, R. F.: Fatal Anaphylactic Reaction Following Penicillin Injection, U. S. Armed Forces M. J. **4**:249-252, 1953. Higgins, G. A., and Rothchild, T. P. E.: Fatal Anaphylactic Shock from Procaine Penicillin, New England J. Med. **247**:644-646, 1952. Mayer, P. S.; Mosko, M. M.; Schutz, P. J.; Osterman, F. A.; Steen, L. H., and Baker, L. A.: Penicillin Anaphylaxis, J. A. M. A. **151**:351-353, 1953. Siegal, S.; Steinhardt, R. W., and Gerber, R.: Fatal and Near-Fatal Penicillin Anaphylaxis, J. Allergy **24**:1, 1953. Thomson, W. O.: Sudden Death Following an Injection of Penicillin, Brit. M. J. **2**:70-72, 1952.

is reported to be of value in anaphylactic and other histamine-like reactions[39] but could not be expected to be effective in sensitivity manifestations of a different type.[40] Corticotropin (ACTH) and cortisone have also been advised, and their use will be discussed elsewhere. Staphylococcus toxoid has been suggested for the treatment of penicillin urticaria.[41]

Certain antibiotics, particularly chloramphenicol, appear to be toxic to the hematopoietic system, causing leucopenia and an aplastic anemia, which may be fatal.[42] In the absence of experimental data, it is difficult to be certain that any particular agent is the cause of an aplastic anemia. Yet the weight of evidence supports the view that chloramphenicol was the myelotoxic substance in the vast majority of the cases in which the condition was attributed to it. The bone marrow depression may follow prolonged administration (weeks to months) of small or large doses, or it may occur after only a short course of therapy, reckoned "in hours rather than in days or weeks."[43] In cases of the latter type a history of prior treatment with the drug may be elicited, and the patient may show an intolerance, such as nausea and vomiting, upon institution of the second course. A history of an allergy and/or prior ingestion of chloramphenicol should make one circumspect. There is no reported treatment of benefit. Corticotropin, cortisone, and vitamin B_{12} have proved ineffective. Supportive treatment with transfusions is essential. This untoward response to the drug certainly contraindicates its indiscriminate use. However, considering the widespread use of chloramphenicol, the incidence of toxicity is certainly low, and its continued use in those instances in which it may be of proved value appears justified.

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39. Farber, J. E., and Ross, J.: Antibiotic Anaphylaxis, M. Times **80**:28-30, 1952. Maslansky, L., and Sanger, M. D.: A Method of Decreasing Penicillin Sensitivity, Antibiotics & Themother. **2**:385-388, 1952.

40. MacKay, C. R.: Failure of Antihistamine Therapy in Severe Sulfadiazine Hypersensitivity, Rocky Mountain M. J. **49**:441-442, 1952.

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43. Hargraves, M. M.; Mills, S. D., and Heck, F. J.: Aplastic Anemia Associated with the Administration of Chloramphenicol, Proc. Staff Meet., Mayo Clinic **27**:280-281, 1952.

Blood dyscrasias from use of sulfonamides continue to be reported.[44] It has been suggested that certain antibiotics alter the coagulability of blood, but this has been rather well disproved.[45]

Severe gastrointestinal disturbances may follow the use of antibiotics, particularly after oral administration of the broad-spectrum antibiotics; aureomycin, chloramphenicol, and oxytetracycline. These disturbances may involve all portions of the gastrointestinal tract.[46] They are considered to be due to local irritation, alteration of the bacterial flora, or hypersensitivity. Salt depletion due to diarrhea may occur.[47] Avitaminosis B, due to sterilization of the bowel, has been suggested, but it is probably minor in degree.[48] Aureomycin and oxytetracycline, particularly the former, have a certain hepatotoxic action, but this has not been shown to be of any clinical importance.[49]

Certain antibiotics, particularly the polypeptides, are nephrotoxic. These include bacitracin, neomycin, and the polymyxins, of which polymyxins B and E are the least toxic. It is interesting that certain transmethylating agents, such as methionine and choline, protect the kidney of the rat from the toxic effects of polymyxin A.[50] Transient polyuria and proteinuria may result from the parenteral administration of polymyxin B (aerosporin),[51] but this does not appear to be cause for cessation of therapy, since they readily disappear when treatment is discontinued and are not indicative of permanent renal damage.

The neurotoxic effect of streptomycin on the eighth cranial nerve is well known.[52] A neurotoxic reaction to chloramphenicol, manifested by optic neuritis and peripheral neuritis, has been reported.[53] Two cases of transient myopia with reduced

44. Geiger, J.: Thrombocytopenic Purpura Induced by Sulfisoxazole (Gantrisin®) Therapy, J. A. M. A. **149**:1219-1220, 1952. Gilbert, F. I., Jr., and Arnold, H. J., Jr.: Failure of Corticotropin to Prevent Acute Hemolytic Anemia Due to Sulfapyridine, ibid. **150**:95-96, 1952.

45. Ingram, G. I. C., and Armitage, P.: Effect of Penicillin and of Streptomycin on Blood Coagulation in Normal Subjects, J. Pharm. & Pharmacol. **4**:1047-1062, 1952. Parker, J. W., Jr., and Wright, L. T.: Effect of Terramycin and Aureomycin on Blood Coagulation, Science **116**:282-284, 1952.

46. Brown, R. L.: The Gastrointestinal Tract and Stool Following Aureomycin Therapy, Antibiotics & Chemother. **2**:5-11, 1952. Reiner, L.; Schlesinger, M. J., and Miller, G. M.: Pseudomembranous Colitis Following Aureomycin and Chloramphenicol, A. M. A. Arch. Path. **54**:39-68, 1952.

47. Catanzaro, F. J.; Ostfeld, A. M., and Bergner, G. E.: Low Salt Syndrome During Treatment with Chloramphenicol, J. A. M. A. **149**:571-572, 1952.

48. Sarett, H. P.: Effect of Oral Administration of Streptomycin on Urinary Excretion of B Vitamins in Man, J. Nutrition **47**:275-287, 1952.

49. Bateman, J. C.; Barberio, J. R.; Cromer, J. K., and Klobb, C. T.: Investigation of Mechanism and Type of Jaundice Produced by Large Doses of Parenterally Administered Aureomycin, Antibiotics & Chemother. **3**:1-16, 1953. Cutting, W. C.: Liver Changes Produced by Aureomycin and Terramycin, Stanford M. Bull. **10**:18, 1952. Rutenburg, A. M., and Pinkes, S.: Hepatotoxicity of Intravenous Aureomycin, New England J. Med. **247**:797-800, 1952.

50. Short, E. L.: Mechanism of Methionine Protection Against the Nephrotoxicity of Polymyxin A, Brit. J. Pharmacol. **7**:248-254, 1952.

51. Light, A. E.; Tornaben, J. A., and DeBeer, E. J.: Comparison of the Renal Effects of Polymyxin A, Aerosporin and a Mercurial Diuretic, Antibiotics & Chemother. **2**:63-71, 1952.

52. Don, C., and Gregory, J.: Toxicity of Dihydrostreptomycin Sulphate for the Auditory Nerve, Lancet **1**:72-75, 1952. Naismith, J. T.: Deafness with Use of Dihydrostreptomycin in Tuberculous Meningitis, Brit. M. J. **1**:796-798, 1952.

53. Wallenstein, L., and Snyder, J.: Neurotoxic Reaction to Chloromycetin, Ann. Int. Med. **36**:1526-1527, 1952.

accommodation following sulfonamide therapy have been reported, the author[54] suggesting that the cause was allergic edema of the ciliary body.

The newer antibiotics, erythromycin and magnamycin, appear to have low toxicity.[55]

Clinical Use of Antibiotics and Sulfonamides.—In the various reviews on the use of antibiotics and sulfonamide drugs,[56] certain precautions and suggestions are stressed. These constitute no startling revelations but merit repetition here. First, the indiscriminate use of these agents is to be avoided. Second, whenever feasible, the organism should be cultured and its sensitivity to antibiotics determined. Third, unless sensitivity findings give a contrary indication, local use of antibiotics should be restricted to those drugs that do not have a widespread use systemically and only rarely produce hypersensitive reactions. These include such agents as neomycin, bacitracin, and polymyxin B. Neomycin, in particular, has been found to be valuable for local application, since it has a rather wide spectrum and only rarely invokes a hypersensitivity response.[57] The 1-ephenamine salt of crystalline penicillin has been claimed to have hypoallergenic properties, and in a report of its local use in the treatment of pyoderma no instance of the development of hypersensitivity[58] was recorded.

Lastly, the question of the prophylactic use of antibiotics has no dogmatic answer. The problem of toxicity and the possibility of the emergence of a resistant strain must be weighed against the benefits that might be expected from such use. In cases in which there has been an intraocular penetration of a foreign body, the prophylactic use of these agents has been strongly urged,[59] particularly because disastrous sequelae develop rapidly once an infectious process takes hold. No particular agent or combination of agents can categorically be stated to be preferable for this use. Combinations of penicillin and streptomycin or the sulfonamides may have merit (see discussion of the value of the use of combinations of these agents below), as may one of the broad-spectrum antibiotics used alone. Incidentally, the fact that many antibiotics (penicillin, aureomycin, and oxytetracycline) may protect

54. Mattsson, R.: Transient Myopia Following the Use of Sulphonamides, Acta ophth. **30**: 385-398, 1952.

55. Heilman and others.[27] Gardocki, J. F., and others: Magnamycin: Toxicity in Experimental Animals, Antibiotics & Chemother. **3**:55-63, 1953.

56. Brown, R. K.: Influence of Modern Antibiotics on Abdominal Surgery, New York J. Med. **53**:171-175, 1953. Lawrence, F. S.: Present Role of the Sulphonamides, Practitioner **168**: 180-190, 1952. Macdonald, J. B.: Principles of Antibiotic Therapy, J. Canad. Dent. A. **18**:458-463, 1952. Patterson, R. H., and Bromberg, B.: Influence of Antibiotics in the Surgical Treatment of Injuries and Infections of the Extremities, New York J. Med. **53**:176-181, 1953. Shea, J. J., and Shea, J. J., Jr.: Use and Abuse of the Antibiotics in Otolaryngology, Eye, Ear, Nose & Throat Month. **31**:647-651, 1952. Waisbren, B. A.: A Point of View in Regard to the Use of Antibiotics, Marquette M. Rev. **17**:51-57, 1952.

57. Forbes, M. A., Jr.: A Clinical Evaluation of Neomycin in Different Bases, South. M. J. **45**:235-239, 1952. Kile, R. L.; Rockwell, E. M., and Schwarz, J.: Use of Neomycin in Dermatology, J. A. M. A. **148**:339-343, 1952. Livingood, C. S.; Nilasena, S.; King, W. C.; Stevenson, R. A., and Mullins, J. F.: Pyogenic Infections Treated with Neomycin, ibid. **148**:334-339, 1952. Ravina, A.: Une nouvelle indication, peut-être primordiale, de la néomycine: Le traitment des infections cutanées, Presse, méd. **60**:1237-1238, 1952.

58. Rattner, H., and Rodin, H. H.: Treatment of Pyodermas with Penicillin 92: Comparison with Neomycin and Bacitracin, A. M. A. Arch. Dermat. & Syph. **65**:656, 1952.

59. Leopold, I. H.: Surgery of Ocular Trauma, A. M. A. Arch. Ophth. **48**:738-746, 1952.

against clostridial infections[60] does not mean that the use of tetanus antitoxin or toxoid is to be discarded. The value of the routine preoperative use of antibiotics (systemic or local) in the absence of recognizable infection is still debated. The emergence of resistant strains, particularly Gram-negative organisms, may be a serious problem, as a recent report on panophthalmitis following cataract surgery has emphasized.[61] Whether the preoperative use of these antimicrobial agents may actually promote the emergence of these strains cannot be stated. At the same time, the incidence of infection from the common skin contaminants, such as the staphylococci, may be reduced and the over-all occurrence of panophthalmitis lowered.

From what has been said, it is apparent that the choice of antibiotic for the treatment of ocular infections will depend on many factors, e.g., the organism and its sensitivity, the route of administration (local or systemic), and a history of drug sensitivity. In many instances several agents may appear equally valuable. A word concerning the choice of sulfonamide drugs is advisable at this point. So far as their antibacterial spectrum is concerned, there is little difference in the sulfonamides. Moreover, when they are prescribed in recommended dosage, the toxicities of the sulfonamides in common use at present are similar. The sulfonamides differ, however, in their distribution in body fluids, and on this fact hinges the choice of agent. The pyrimidine derivatives of sulfanilamide, e.g., sulfadiazine, sulfamerazine, and sulfamethazine, pass the hematocephalic barriers best and are the sulfonamides of choice if intraocular penetration from the blood stream is desired. On the other hand, sulfonamide drugs such as sulfisoxazole (Gantrisin), an isoxazole derivative, penetrate the hematocephalic barriers less readily but are excreted in higher concentration in the urine, and thus are valuable in the treatment of infections of the urinary tract.[62] Sulfacetimide, one of the oldest of the sulfonamide drugs, is rather widely used as a local agent in ophthalmology. The successful use of 4% sulfisoxazole locally in external ocular disease has been reported.[63]

The more resistant bacterial strains deserve comment. The penicillin-resistant staphylococci may respond to the broad-spectrum antibiotics. The newer agents, erythromycin and magnamycin, have spectrums much like penicillin and may also be effective.[64] Bacitracin must not be overlooked and may be used systemically

60. Kiser, J. S.; de Mello, G. C.; Reichard, D. H., and Williams, J. H.: Chemotherapy of Experimental Clostridial Infections, J. Infect. Dis. **90**:76-80, 1952. Sandusky, W. R.; Keeble, C. F.; Wharton, W. P., and Taylor, R. N.: Prophylactic Use of Terramycin in Experimental Clostridium Welchii Infection in Guinea Pigs, Surgery **31**:365-366, 1952. Taylor, W. I., and Novak, W.: Antibiotic Prophylaxis of Experimental Clostridial Infections: I. Antibiotic Prophylaxis of Tetanus, Antibiotics & Chemother. **2**:517-520, 1952; II. Penicillin Prophylaxis of Clostridium Perfringens and Clostridium Septicum Infections, ibid. **2**:576-580, 1952.

61. Callahan, A.: Effects of Sulfonamides and Antibiotics on Panophthalmitis Complicating Cataract Extraction, A. M. A. Arch. Ophth. **49**:212-219, 1953.

62. Lehr, D.: Comparative Merits of 3,4-Dimethyl-5-Sulfanilamide-Isoxazole (Gantrisin) and a Sulfapyrimidine Triple Mixture, Antibiotics & Chemother. **3**:71-94, 1953.

63. Warren, C. M., Jr.: Local Treatment of Eye Infections with Gantrisin, South. M. J. **45**:1183-1185, 1952.

64. English, A. R.; Mullady, H. E., and Fitts, R. A.: Magnamycin: II. In Vivo Studies, Antibiotics & Chemother. **3**:94-98, 1953. Haight, T. H., and Finland, M.: Laboratory and Clinical Studies on Erythromycin, New England J. Med. **247**:227-232, 1952; Resistance of Bacteria to Erythromycin, Proc. Soc. Exper. Biol & Med. **81**:183-188, 1952. Tanner, F. W., Jr.; English, A. R.; Lees, T. M., and Routien, J. B.: Some Properties of Magnamycin, A New Antibiotic, Antibiotics & Chemother. **2**:441-443, 1952. Trafton, H. M.; Lind, H. E., and Correia-Branco, M.: Treatment of Urinary-Tract Infections with a New Antibiotic—Magnamycin, New England J. Med. **248**:379-380, 1953.

with success when other agents have failed.[65] The treatment of Proteus infections may be more difficult. Streptomycin and the sulfonamides are the time-honored agents of choice. Polymyxin B and neomycin are perhaps helpful, as may be the broad-spectrum antibiotics. Pseudomonas infections are reported to be best treated by polymyxin B.[66] While failure to control experimental ocular infection due to Ps. aeruginosa with polymyxin B has been reported,[67] the evidence is good that on the whole polymyxin B and polymyxin E are the antibiotics of choice in the treatment of ocular infections due to this organism.[68] Beneficial results from the local combined use of polymyxin B and streptokinase-streptodornase (Varidase) on a corneal abscess due to Ps. aeruginosa in man have been reported,[69] previous therapy with penicillin, aureomycin, chloramphenicol, and streptomycin having failed. The broad-spectrum antibiotics and streptomycin, however, may be of value.[70] In the final analysis, adequate therapy can be dictated only by sensitivity tests.

Against other infections, the use of specific antibiotics appears more predictable. Streptococcic, pneumococcic, and gonococcic infections generally respond well to penicillin, the sulfonamides, and the broad-spectrum antibiotics. The treatment of conjunctivitis due to the Koch-Weeks organism with a mixture of polymyxin B and oxytetracycline has been recommended.[71] Infection with the Gram-negative bacilli not previously mentioned, particularly Escherichia coli and Aerobacter aerogenes, usually respond to the broad-spectrum antibiotics.[72] Streptomycin, the sulfonamides, neomycin, and the polymyxins may be helpful in the treatment of infections

65. Charet, R., and Siegel, I.: Acute Staphylococcic Lung Abscess Cured with Aid of Bacitracin, A. M. A. Arch. Int. Med. **90**:250-257, 1952. Meleney, F. L.; Johnson, B. A., and Teng, P.: Further Experiences with Local and Systemic Bacitracin in the Treatment of Various Surgical and Neurosurgical Infections and Certain Related Medical Infections, Surg., Gynec. & Obst. **94**:401-425, 1952.

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due to these organisms. Chloramphenicol is the drug of choice in typhoid,[73] as is streptomycin in tularemia.[74]

Penicillin remains the preferred antibiotic in the treatment of syphilis, acquired and congenital.[75] The broad-spectrum antibiotics, particularly aureomycin and oxytetracycline, are probably less effective but may be helpful where hypersensitivity to penicillin has been established.[76] Treatment with penicillin has been found to arrest the visual loss resulting from syphilitic optic nerve atrophy in patients whose initial vision was 20/50 or better, but the response is otherwise poor.[77] An apparent cure (judged by seronegativity) of congenital syphilis treated in infancy with penicillin may not prevent the development of interstitial keratitis at a later date.[78]

In the treatment of ocular tuberculosis, streptomycin, alone or with adjuvant therapy, is the drug of choice,[79] although success may be variable. Reports of successful treatment of conjunctival tuberculosis by local application of streptomycin and of miliary choroidal tuberculosis by systemic use have appeared. Oxytetracycline has been found to be inferior to streptomycin in the treatment of experimental ocular tuberculosis.[80] This mirrors clinical impression of the use of this drug in the treatment of tuberculous lesions of other tissues.[81]

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In the treatment of pulmonary and other tuberculous infections at least two groups of antituberculous agents have shown real promise.[82] The first group includes *p*-aminosalicylic acid, which has emerged as a valuable adjuvant to therapy. It has antituberculous activity when used alone, and, perhaps more important, it markedly reduces the development of resistance to streptomycin when used in conjunction with the latter drug.[83] Paraaminosalicylic acid has been shown to have antithyroid activity,[84] hyperplasia of the thyroid gland resulting. A case of exophthalmos with thyroid enlargement following treatment with this drug has been reported.[85] The current trend in therapy is to combine the daily use of *p*-aminosalicylic acid (12 gm.) with parenteral administration of streptomycin, the latter being given only two or three times weekly, in 1 gm. doses.[86]

One of the striking advances of the year in the treatment of tuberculosis has been the development of isonicotinic acid hydrazide and its isopropyl derivative, whose use as antituberculous agents was first reported early in 1952.[87] Outstanding among the early benefits of the drug appear to be the elimination of fever, gain in weight, and a general feeling of well-being. A clinical comparison of isonicotinic acid hydrazide therapy alone and streptomycin plus *p*-aminosalicylic acid therapy showed that, over the period of observation, isonicotinic acid hydrazide therapy was as good as, and perhaps better than, the streptomycin-*p*-aminosalicylic-acid regimen.[88] The possibility of a relapse after prolonged therapy with isonicotinic acid hydrazide, however, has been suggested.[89] Resistance of the tubercle

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bacillus to isonicotinic acid hydrazide does develop during therapy, but there appears to be no cross resistance between this drug and streptomycin.[90] Isonicotinic acid hydrazide shows high specificity in vitro for the tubercle bacillus[91] and has little activity against other bacteria. The existence of resistant strains of Mycobacterium tuberculosis which have had no previous contact with the drug have been reported.[92] The mode of action of isonicotinic acid hydrazide is not certain. The drug appears to alter the metabolism of the tubercle bacillus.[93] Reported toxic effects of the drug include hyperreflexia, leg twitching, constipation, vertigo, reflex disturbances of micturition, sensory disturbances, cutaneous allergy from local contact, and withdrawal symptoms.[94] They do not appear to be serious except when renal damage impairs excretion of the drug.[95] A synergistic action of isonicotinic acid hydrazide, streptomycin, and *p*-aminosalicylic acid has been suggested from in vitro studies and clinical observations.[96] When a combination of any two of the three drugs is used, development of bacterial resistances to both agents appears to be delayed. A therapeutic plan which is being evaluated at present is the combined use of streptomycin in 1 gm. doses two or three times a week with administration of isoniazid in daily doses of 150 to 200 mg. and *p*-aminosalicylic acid in daily doses of 10 to 12 gm. The therapeutic efficacy of this regimen remains to be determined.

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The Rickettsial diseases respond to the broad-spectrum antibiotics both in vivo and in vitro.[97] The value of antibiotics in the treatment of parasitic infections is variable. In some instances they may be beneficial.[98]

As a general rule, it can be stated that viral diseases do not respond to the common antibiotics or sulfonamides. This is supported by a large volume of reported therapeutic failures in a variety of clinical and experimental virus infections,[99] including primary vaccinia of the eyelid [100] and herpes zoster.[101] It is likely that the clinical benefits ascribed to the antibiotics in these diseases are due to the control of secondary infection. The psittacosis group of viruses is another matter, however. There is reasonably good evidence that many of the antibiotics, as well as the sulfonamides, may alter the course of clinical and experimental infections caused by these large viruses.[102] The viruses of trachoma and inclusion blennorrhea fall within this group. There have been several reports on the use of oxytetracycline, aureomycin, and sulfonamides in the treatment of trachoma.[103] Conclusions con-

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cerning their merit are guarded. Most authors agree that the sulfonamides and the broad-spectrum antibiotics are equally effective, that none of these agents is curative when used alone, that one of the important actions of these agents is the control of secondary infections, and that mechanical measures should not be discarded. The use of combined sulfadiazine and diphenhydramine (Benadryl) therapy in trachoma with hyperplastic conjunctival lesions has been reported to give both subjective and objective improvement.[104]

Infection with the pseudofungus Actinomyces has been reported to respond to chloramphenicol and penicillin.[105] One of the hazards of antibiotic therapy, however, is the emergence of a fungous infection. As would be expected, therefore, the widely used antibiotics and sulfonamides have only limited, if any, activity against the true fungi. The polymyxins may inhibit certain fungi, including C. albicans.[106] Other antibiotics show more promise as fungicidal agents.[107] An excellent review of mycotic infections of the eye, including treatment, has appeared during the past year.[108]

Combinations of Antibiotics and Sulfonamides in Clinical Use.—The question of the clinical efficacy of the use of combinations of antibiotics and of the reproducibility of response is difficult to answer. Beneficial effects of some combinations appear to be more adequately demonstrated than others. A mixture of polymyxin B and bacitracin in an ointment for local use has the advantage of combining an agent predominantly effective against Gram-negative organisms with one which maximally inhibits Gram-positive bacteria.[109] The combined use of penicillin and the sulfonamides is said to be more effective than the use of either alone.[110] Use of combining sulfonamides is said to reduce antibacterial potency.[111] A synergism of penicillin with either streptomycin or bacitracin and an antagonism between peni-

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cillin and the broad-spectrum antibiotics have frequently been suggested and can be demonstrated experimentally.[112] There is, however, no set rule, and clinical experience has at times indicated that the broad-spectrum agents may be synergistic with penicillin, streptomycin, or polymyxin B.[113] The work of Jawetz and his associates[114] appears to be clearing the field. They state[115]:

> Perhaps the most important feature is the variation in the response of microbial strains to drug combinations. This emphasizes the impossibility of labeling certain drug pairs as "synergistic" or "antagonistic," and stresses the desirability of laboratory guidance in those occasional difficult situations where drug combinations are essential for cure.

Other Chemotherapeutic Agents

Nitrofurazone (Furacin) is one of a group of nitrofuraldehydes which has limited antibacterial potency. It may act by altering certain enzyme sulfhydryl groups in susceptible bacteria.[116] Sensitive bacteria acquire only limited resistance to the drug in vitro, and no cross resistance between the nitrofurazones and chloramphenicol or aureomycin has been noted.[117] The use of nitrofurazone has been reported to be of benefit in external ocular disease caused by a variety of organisms, mostly staphylococci.[118] The compound was well tolerated. The allergic incidence was stated to be less than 1%. Its role in the control of ophthalmic infections, however, needs more study.

Sodium propionate has some activity as an antimicrobial and antifungal agent in high concentrations, perhaps because of its influence on the carbohydrate metabolism of the organism.[119] It is said to be hypoallergenic and virtually nonirritating in therapeutic concentrations.[120]

The use of silver compounds in the prophylaxis of ophthalmia neonatorum continues to be widespread in the United States, and probably will remain so.[121] The

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120. Heseltine, W. W.: A Note on Sodium Propionate, J. Pharm. & Pharmacol. **4**:120-122, 1952.

121. Prophylaxis of Ophthalmia Neonatorum, Editorial, J. A. M. A. **148**:122-123, 1952.

British Ministry of Health has recently published an interesting account of a survey made among some 250 maternity hospitals and a slightly smaller number of local health authorities.[122] The results of this survey indicated that in over one-half the hospitals chemical prophylaxis had been abandoned completely. In many of the remaining hospitals silver preparations had been replaced by some other agent, such as penicillin. The survey indicated that the incidence of ophthalmia neonatorum was no higher, and in many cases was actually lower, when silver preparations were not used, whether or not another prophylactic agent was substituted. No cultures were made, however, the survey being exclusively clinical.

This list of chemotherapeutic agents is by no means complete. Many others, such as the diamidines, continue to be studied,[123] and their inclusion in future reviews may be essential.

CORTICOTROPIN, CORTISONE, AND HYDROCORTISONE

When cortisone and corticotropin were introduced into clinical medicine, some four years ago, the physician found himself in the rather peculiar position of having available potent agents the pharmacology of which was little understood. In addition, they were effective against a variety of disease processes the exact etiology of which was uncertain. From such a combination of negatives, it is no wonder that conflicting reports of the merit of the hormones in many clinical conditions have appeared. Yet, from the large volume of published material, the therapeutic value of these agents is gradually crystallizing. Moreover, during the intervening years these hormones have been employed in a variety of experimental studies designed to determine their general metabolic and tissue effects and thus to put clinical usage on a firmer footing. To complete the circle, the clinical and experimental studies of corticotropin and cortisone have contributed to knowledge of the pathogenesis of certain disease processes. As Thorn[124] puts it:

> Important as the adrenal secretions appear to be clinically as protective agents . . . their ultimate contribution to knowledge and health will undoubtedly be correlated much more closely with the opportunities which they have provided for exploring intimate biological processes in a wide variety of pathological conditions than with their usefulness in the correction of any specific disease process.

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122. Elliott, R. A.: Ophthalmia Neonatorum: A Review of Prophylactic Methods at Present in Use, Month. Bull. Min. Health **11**:135-137, 1952.

123. Eaton, M. D.; Levenson, C. G., and Perry, M. E.: Inhibition of the Growth of Viruses in the Chick Embryo by Aromatic Diamidines, J. Immunol. **68**:1-9, 1952. Eaton, M. D.; Perry, M. E.; Levenson, C. E., and Gocke, I. M.: Studies on the Mode of Action of Aromatic Diamidines on Influenza and Mumps Virus in Tissue Culture, ibid. **68**:321-334, 1952. Heilman, F. R.: Effect of Stilbamidine on Blastomycosis in Mice, Proc. Staff Meet., Mayo Clinic **27**:455-458, 1952. Miller, J. M.; Schoenbach, E. B.; Long, P. H.; Shuttleworth, J. S., and Snider, G. E.: Treatment of Infections Due to Cryptococcus Neoformans with Stilbamidine, Antibiotics & Chemother. **2**:444-446, 1952. Miller, J. M.; Long, P. H., and Schoenbach, E. B.: Successful Treatment of Actinomycosis with "Stilbamidine," J. A. M. A. **150**:35, 1952. Schoenbach, E. B.: Use of the Aromatic Diamidines for the Treatment of Systemic Fungal Disease, Tr. New York Acad. Sc. **14**:272-273, 1952. Snapper, I.; Schneid, B.; McVay, L., and Lieben, F.: Pharmacology and Therapeutic Value of Diamidine Derivatives—Particularly 2-Hydroxystilbamidine, ibid. **14**:269, 1952.

124. Thorn, G. W.: The Adrenals in Health and Disease, Tr. & Stud. Coll. Physicians Philadelphia **19**:95-113, 1952.

An excellent and comprehensive review of the pharmacology of these hormones has recently appeared.[125] The present review is an endeavor to assemble those current studies of the physiologic response to these agents under normal and pathologic or experimental situations which may supply direction to their clinical use in ophthalmology. A consideration of the equally important problem of sifting and analyzing statistically the results of their use in a variety of ocular diseases is not included but can be found elsewhere.[126]

General Nature of the Hormones.—Corticotropin (adrenocorticotropic hormone; ACTH) is elaborated by the pituitary gland under the influence of the hypothalamus. Secretion of the hormone is increased under certain conditions, given the categorical name "stress." Corticotropin is generally considered to be a protein, although a simple polypeptide with considerable activity has been isolated. Probably the polypeptide forms a loose combination with a protein. By most measures corticotropin polypeptide is not quite so active biologically as the protein combination.[127] Corticotropin disappears from the blood stream rather quickly, apparently being inactivated by some heat-labile constituent of plasma.[128] Isotopically marked hormone can be identified in the adrenal cortex. Here it stimulates the synthesis of the steroid hormones, in addition to promoting the release of preformed material.[129] The physiologic effect of corticotropin depends upon the release of the corticosteroids.

To date, approximately 30 steroid hormones have been isolated from the adrenal cortex, and the list is not complete, since this gland contains some as yet unidentified substances with potent metabolic activity.[130] The three corticosteroids of greatest clinical usefulness and interest are desoxycorticosterone (11-desoxycorticosterone), cortisone (11-dehydro-17-hydroxycorticosterone), and hydrocortisone (17-hydroxycorticosterone). The first compound has a potent effect on the electrolyte and water balance, and its clinical usefulness is chiefly limited to replacement therapy in adrenal insufficiency. Since it does not have the anti-inflammatory effects of cortisone and hydrocortisone, it will not be considered in this review.

It is now well recognized that hydrocortisone is the principal corticosteroid released from the adrenal cortex under stimulation by corticotropin. Cortisone is also released but in considerably smaller quantities. The normal value for the 17-hydroxycorticosteroids in human peripheral blood lies between 4 and 10 γ per

125. Thorn, G. W.; Jenkins, D.; Laidlaw, J. C.; Goetz, F. C.; Dingman, J. F.; Arons, W. L.; Streeten, D. H. P., and McCracken, B. H.: Medical Progress: Pharmacologic Aspects of Adrenocortical Steroids and ACTH in Man, New England J. Med. **248**:232, 284-294, 323-337, 369-378 and 414-423, 1953.

126. Berens, C., and Bickerton, J. H.: Review of the Results of Cortisone and ACTH Therapy in Diseases of the Eye, Quart. Rev. Ophth. **8**:77-86, 1952.

127. Ingle, D. J., and Li, C. H.: Comparison of Biologic Effects of ACTH Protein and ACTH Peptide Given by Continuous Injection, Proc. Soc. Exper. Biol. & Med. **79**:128-131, 1952.

128. Pincus, G.; Hopkins, T. F., and Hechter, O.: An ACTH-Inactivating Factor in Mammalian Blood, Arch. Biochem. **37**:408-418, 1952.

129. Haynes, R.; Savard, K., and Dorfman, R. I.: An Action of ACTH on Adrenal Slices, Science **116**:690-691, 1952.

130. Pfiffner, J. J.: Adrenal Cortical Hormones, Advances Enzymol. **2**:325-356, 1942.

100 ml.[131] The biologic relation between the two is not firmly established, but it is suggested that cortisone and hydrocortisone may exist in reversible equilibrium with one another.[125] For the present, it is justifiable to consider the two compounds as having physiologic activity, qualitatively the same but quantitatively different, hydrocortisone being almost twice as potent as cortisone. In the vast majority of studies on the effect of these agents cortisone has been employed.

Metabolic Effects.—That the adrenal gland may play an important role in the carbohydrate metabolism has been known since the observation of Long and Lukens that adrenalectomy ameliorated the diabetes of the depancreatized animal. Prolonged administration of corticotropin, cortisone, and hydrocortisone may give rise to a condition termed "steroid diabetes." This may manifest itself as a diminished tolerance to glucose—a glucosemia, a glucosuria, and an increased glycogen deposition in the liver and muscle. The cause of this disturbance appears to be largely an overproduction of glucose, mostly from protein, although the possibility of increased gluconeogenesis from fat cannot be excluded.[132] This is the form of diabetes seen in Cushing's syndrome.[133] As the drugs are usually employed clinically, however, the diabetic tendency is not particularly pronounced,[134] although a familial tendency to this metabolic disturbance may be unmasked. Upon cessation of hormone therapy, the hyperglycemia and glucosuria disappear. In diabetic patients, the increased gluconeogenesis can be compensated for by increased administration of insulin.

A relationship between diabetic retinopathy and the steroid hormones is sufficiently suggestive to require mention. In steroid diabetes ketonuria and acidosis rarely develop. An analysis of the histories of patients with diabetic retinopathy indicated that this pathologic condition more frequently is seen in patients who have no clinical record of ketonuria and acidosis.[135] Thus, it has been suggested that these hormones may have some relation to the production of the capillary aneurysms of the diabetic retina.[136] The experimental production of the aneurysmal lesions in alloxan-induced diabetes in the rabbit given corticotropin lends further credence to this view. Corticotropin and cortisone have been found to be of no benefit in the treatment of diabetic retinopathy. The thoughts here reported suggest that they may actually be contraindicated.

131. Nelson, D. H., and Samuels, L. T.: Method for Determination of 17-Hydroxycorticosteroids in Blood: 17-Hydroxycorticosterone in the Peripheral Circulation, J. Clin. Endocrinol. **12**:519-526, 1952.

132. Kinsell, L. W.; Michaels, G. D.; Margen, S.; Boling, L., and Partridge, J. W.: Evidence for Acceleration of Neoglucogenesis from Fat by ACTH, Cortisone and Related Compounds, J. Clin. Endocrinol. **12**:945, 1952.

133. Hills, O. W.; Power, M. H., and Wilder, R. M.: Diabetes Mellitus and Cushing's Syndrome, Diabetes **1**:351-357, 1952.

134. Appel, S. B., and Orr, K. D.: Observations on Essentially Normal Young Men Treated with ACTH and Cortisone: I. Effects on Glucose Metabolism, U. S. Armed Forces M. J. **3**:207-219, 1952. Bookman, J. J.; Drachman, S. R.; Schaefer, L. E., and Adlersberg, D.: Studies on Steroid Diabetes in Man, J. Clin. Endocrinol. **12**:945-946, 1952. Jackson, R. S., and Fabrykant, M.: Early Effects of ACTH on Arterial and Venous Blood Glucose and on Renal Glucose Excretion, Am. J. Digest. Dis. **19**:329-332, 1952.

135. Dana, G.; Eversole, S., and Zubrod, C.: Clinical Entity of Retinal Aneurysms, Glomerular Nodules and Hyperglycemia, Bull. Johns Hopkins Hosp. **90**:323-326, 1952.

136. Becker, B.: Diabetic Retinopathy, Ann. Int. Med. **37**:273-289, 1952. Friedenwald, J. S.: Diabetic Retinopathy, J. A. M. A. **150**:969-971, 1952.

The catabolic effect of corticotropin and cortisone on protein is well known. Administration of large doses of these hormones may send the patient into a negative nitrogen balance unless he is protected by a high protein diet or other dietary measures. These hormones may be antianabolic as well. An increase in urea formation [137] and a decrease in protein content of the liver in the experimental animal [138] are measures of these effects. The hormones also inhibit growth. As previously mentioned, this inhibition can be overcome if aureomycin and vitamin B_{12} are fed in addition.

No conclusion can be drawn at present concerning the effects of these hormones on fat metabolism, particularly in man. It has been suggested that a rise in cholesterol may follow prolonged administration of both corticotropin and cortisone and that this may be associated with increased atherosclerosis. An increased lipid deposition in the arteries of persons under 11 years has been reported to follow cortisone administration, although above this age no significant difference could be determined.[139] Moreover, hypercholesteremia is only variably produced, and the lipoprotein complexes of the size supposedly associated with atherosclerosis do not increase.[140]

Administration of cortisone or corticotropin is followed by a retention of sodium and an increased excretion of potassium. Hydrocortisone has a more pronounced effect on the electrolyte balance than does cortisone, although neither is as potent as desoxycorticosterone. The retention of sodium which corticotropin induces can be counteracted by mercurial diuretics.[141] Changes in the electrolyte concentration are not limited to the extracellular phase, however. The cellular potassium may decrease and the cellular sodium rise. The depletion of body potassium may be partly due to the breakdown of cellular protein and loss of cellular phosphorus, but the ultimate explanation will probably not be so simple. It is interesting to note that the addition of potassium chloride to the diet inhibits the protein-catabolic effect of the steroid hormones and the diabetes-enhancing effects of corticotropin.[142] The changes in electrolyte balance that these hormones induce are accompanied by an increase in the extracellular and a decrease in the intracellular water.[143] It

137. Engel, F. L.: On the Nature of the Interdependence of the Adrenal Cortex, Non-Specific Stress and Nutrition in the Regulation of Nitrogen Metabolism, Endocrinology **50**: 462-477, 1952.

138. Morrison, J. F.: Effect of Adrenocorticotrophic Hormone and Growth Hormone on the Fat, Water and Protein Content of Mouse Liver, Australian J. Exper. Biol. & M. Sc. **30**:313-317, 1952.

139. Etheridge, E. M., and Hoch-Ligeti, C.: Lipid Deposition in Aortas in Younger Age Groups Following Cortisone and Adrenocorticotrophic Hormone, Am. J. Path. **28**:315-318, 1952.

140. Bloom, B., and Pierce, F. T., Jr.: Relationship of ACTH and Cortisone to Serum Lipoproteins and Atherosclerosis in Humans, Metabolism **1**:155-171, 1952.

141. Farah, A. E.: Effects of Desoxycorticosterone and Adrenocorticotrophic Hormone on Mercurial Diuresis, Proc. Soc. Exper. Biol. & Med. **80**:295, 1952.

142. Glafkides, C. M.; Bennett, L. L., and George, G. R.: Inhibition of the Diabetes Enhancing Effect of ACTH by a Diet High in Potassium Chloride, Endocrinology **50**:684-686, 1952. Whitney, J. E., and Bennett, L. L.: Inhibition of the Catabolic Effect of Adrenocorticotrophic Hormone (ACTH) in Rats by a Diet High in Potassium Chloride, ibid. **50**:657-663, 1952.

143. Aikawa, J. K.: Effects of Cortisone Acetate on Fluid and Electrolyte Balance in Normal Rabbits, Proc. Soc. Exper. Biol. & Med. **82**:105-109, 1953. Friis-Hansen, B.; Tudvad, F., and Vesterdal, J.: Effect of ACTH on Body Water Compartment in Juvenile Rheumatoid Arthritis, Scandinav. J. Clin. Lab. Invest. **4**:36-42, 1952.

is not altogether certain, however, that these changes in the fluid compartments are due solely to the altered electrolyte balance. Some more fundamental effect on water distribution seems likely. High doses of cortisone produce a syndrome resembling diabetes insipidus in experimental animals.[144] Of the other mineral changes, an increased excretion of calcium is noted. This may result from a breakdown of the protein matrix of the bone, due to the catabolic action of the hormones, and give rise to osteoporosis.

Effect on Adrenal and Thyroid Gland.—Continuous administration of corticotropin causes hyperplasia of the adrenal cortex. Conversely, cortisone depresses corticotropin production, and continued administration of the steroid results in a decrease in size and function of the adrenal cortex. This is the basis for the treatment of adrenal hyperplasia with cortisone or hydrocortisone.[145] Abrupt cessation of cortisone or hydrocortisone therapy may lead to an adrenal insufficiency of such magnitude as to result in death from shock.[146] For this reason, therapy with the steroids should be tapered off gradually. The adrenal cortex contains a high concentration of ascorbic acid. This drops markedly and with such regularity when the gland is stimulated by corticotropin that the cortical ascorbic acid depletion is used as an assay of corticotropin activity. This measure of activity does not always parallel the other biologic effects, however. Thus, one corticotropin preparation may cause a greater drop in cortical ascorbic acid, but a smaller eosinopenic response, than another.[147] There are many threads of evidence which link ascorbic acid with the pituitary-adrenal axis.[148] Yet adrenocortical function probably is little altered in the scorbutic monkey, although the scorbutic guinea pig shows some evidence of hypofunction of the adrenal gland.[149]

144. Sirek, O. V., and Best, C. H.: Intramuscular Cortisone Administration to Dogs, Proc. Soc. Exper. Biol. & Med. **80**:594-598, 1952.

145. Jailer, J. W.; Louchart, J., and Cahill, G. F.: Diagnostic Considerations and Treatment in Adrenal Virilism, J. A. M. A. **150**:575-579, 1952.

146. Fraser, C. G.; Preuss, F. S., and Bigford, W. D.: Adrenal Atrophy and Irreversible Shock Associated with Cortisone Therapy, J. A. M. A. **149**:1542-1543, 1952.

147. Ingle and Li.[127] Hungerford, G. F.; Reinhardt, W. O., and Li, C. H.: Lack of Correlation of Eosinopenic and Adrenal Ascorbic Acid-Depleting Activities of Various Adrenocorticotropic Preparations, Proc. Soc. Exper. Biol. & Med. **81**:320, 1952.

148. Bacchus, H.; Heiffer, M. H., and Altszuler, N.: Potentiating Effect of Ascorbic Acid on Cortisone-Induced Gluconeogenesis, Proc. Soc. Exper. Biol. & Med. **79**:648-650, 1952. Bacchus, H.; Altszuler, N., and Heiffer, M. H.: Prolongation of Effects of Adrenal Cortical Secretion by Ascorbic Acid: Proposed Mechanism of Action, ibid. **80**:88-91, 1952. Booker, W. M.; Johnson, J. B.; Hayes, R. L.; Thomas, R. F.; Henry, W.; Tureman, J. R., and Bent, F.: Effect of Cortisone on Tolerance to Ascorbic Acid and Level of Blood Cholesterol in Man, J. Clin. Endocrinol. **12**:346-353, 1952. DesMarais, A., and Leblanc, J.: "In Vivo" and "In Vitro" Effect of Ascorbic Acid and ACTH on the Rat Adrenal Cortex, Canad. J. M. Sc. **30**:157-172, 1952. Hughes, C. D.; Swenson, M. J.; Underbjerg, G. K. L., and Hughes, J. S.: Function of Vitamin C in the Adrenal Cortex, Science **116**:252-253, 1952. Stewart, C. P.; Horn, D., and Robson, J. S.: Effect of Cortisone and Adrenocorticotropic Hormone on the Dehydroascorbic Acid of Human Blood Plasma, Biochem. J. **51**:xx, 1952.

149. Banerjee, S., and Chandicharan, D.: Adrenal Cortical Activity in Scurvy, Endocrinology **51**:572-576, 1952. Herrick, E. H.; Mead, E. R.; Egerton, B. W., and Hughes, J. S.: Some Effects of Cortisone on Vitamin C-Deficient Guinea Pigs, ibid. **50**:259-263, 1952. Stewart, C. T.; Salmon, R. J., and May, C. D.: Function of the Adrenal Cortex in Ascorbic Acid Deficiency and Scurvy in the Monkey, J. Lab. & Clin. Med. **40**:657-663, 1952.

The effect of cortisone and corticotropin on the thyroid has been of particular interest because of a possible bearing on exophthalmos. Uptake of radioiodine by the thyroid gland is decreased during cortisone administration.[150] A drop in the protein-bound iodine of the serum is noted. Corticotropin and cortisone, however, do not appear to affect the rate of discharge of thyroid iodine into the blood stream.[151] Generally, then, corticotropin and cortisone do not alter the basal metabolic rate. The reason for this depression of I^{131} uptake is not wholly clear. Secretion of the thyroid-stimulating hormone by the pituitary does not appear to be altered by cortisone, and thyroid-stimulating hormone has its usual stimulating effect on thyroid cells in the presence of cortisone.[152] A more likely explanation is that renal clearance of iodine is increased [153] and the body pool of iodine reduced during cortisone administration. Opinion varies as to the value of cortisone and corticotropin in exophthalmos. They appear to have no effect on experimental exophthalmos [154] in thyroidectomized animals given injections of thyrotropic hormone.

Effect on Formed Elements of the Blood.—One of the most consistent changes seen during administration of corticotropin and cortisone is the drop in the number of eosinophiles in the peripheral blood. The eosinophile count, therefore, serves as a relatively simple laboratory measure of efficacy of therapy. A drop in the eosinophile count in scrapings from the conjunctiva occurring during treatment of allergic conjunctivitis with cortisone has also been noted.[155] However, the eosinophile count tends to return to normal levels after prolonged administration of cortisone.[156] The cause of the eosinopenia is not certain. During corticotropin therapy the eosinophile count of the bone marrow rises.[157] An impaired release of these cells is thus suggested. The hormone, also, may be toxic to the eosinophiles and cause their destruction.[158] Corticotropin has been reported to have no effect in a case of

150. Fredickson, D. S.; Forshan, P. H., and Thorn, G. W.: Effect of Massive Cortisone Therapy on Measurements of Thyroid Function, J. Clin. Endocrin. **12**:541-553, 1952.

151. Albert, A.; Tenney, A., and Ford, E.: Effect of Cortisone and Corticotropin on the Biologic Decay of Thyroidal Radio Iodine, Endocrinology **50**:324-326, 1952.

152. Epstein, D.; Cantarow, A.; Friedler, G., and Paschkis, K. E.: Inhibition of Thyroid Function by Cortisone and ACTH in Hypophysectomized Rats, Proc. Soc. Exper. Biol. & Med. **82**:50, 1953. Halmi, N. S.: Cortisone and Action of Exogenous Thyrotrophin in Hypophysectomized Rats, ibid. **80**:175-176, 1952.

153. Albert, A.; Tenney, A., and Lorenz, N.: Effect of Hypophysectomy on the Renal Clearance of I^{131}, Endocrinology **50**:327-330, 1952. Berson, S. A., and Yalow, R. S.: Effect of Cortisone on the Iodine Accumulating Function of the Thyroid Gland in Euthyroid Subjects, J. Clin. Endocrinol. **12**:407-422, 1952. Kuhl, W. J., Jr., and Ziff, M.: Alteration of Thyroid Function by ACTH and Cortisone, ibid. **12**:554-559, 1952.

154. Dayton, G. O., Jr.: Effect of ACTH on Experimental Exophthalmos, Am. J. Ophth. **35**:101-106, 1952.

155. Hanser, S. A.; Moor, W. A., and Stickle, A. W.: Cytology of Allergic Conjunctivitis, A. M. A. Arch. Ophth. **47**:728-733, 1952.

156. Krebs, G. C., and Holmes, J. H.: The Thorn Test During Cortisone Therapy, Rocky Mountain M. J. **49**:40-43, 1952.

157. Andersson, E.: Effect of ACTH on the Eosinophils in Blood and Bone Marrow, Acta allergol. **5**:52-57, 1952.

158. Padawer, J., and Gordon, A. S.: A Mechanism for the Eosinopenia Induced by Cortisone and by Epinephrine, Endocrinology **51**:52, 1952.

eosinophilic granuloma.[159] Studies showing the particular structure of the steroid molecule essential for maximum eosinopenia have been made.[160]

In addition to the eosinopenia, a lymphopenia is observed to follow the administration of corticotropin and cortisone. It is interesting that both the eosinopenia and the lymphopenia can be prevented by the simultaneous administration of heparin. Again, the exact cause of the lymphopenia is unknown. Cortisone has a direct toxic effect on lymphocytes.[161]

That neutrophilia may follow cortisone administration has been reported frequently. Corticotropin and cortisone are reported to stimulate the development of the myeloid and erythroid elements of the bone marrow.[162] Cortisone also appears to depress the leucopenic response to wide-field irradiation,[163] although recovery of the bone marrow from radiation damage may be impaired.[164] The production of thrombocytes may be stimulated in persons with idiopathic thrombocytopenic purpura,[165] although this probably is not the sole reason for the remission that cortisone may cause in this condition. Corticotropin and cortisone do not cure this disorder but may be of value in the control of bleeding prior to splenectomy, or even following it.[166]

Effect on Skin and Wound Healing.—In Cushing's syndrome the skin is thin and wound healing may be delayed. Corticotropin and cortisone have similar effects on normal skin and subcutaneous tissue. The epidermis is thinned after local administration of cortisone.[167] The number of fibroblasts decreases; the collagen fibers shrink, and the ground substance is reduced in the connective tissue of experimental animals after prolonged administration of the hormones.

The effect of these hormones on wound healing has received considerable attention. It seems likely that these agents may alter the majority of factors involved

159. Henderson, L. L., and Thompson, E. C.: Corticotropin in Eosinophilic Granuloma, J. A. M. A. **151**:294-295, 1953.

160. Halberg, F.: Some Correlations Between Chemical Structure and Maximal Eosinopenia in Adrenalectomized and Hypophysectomized Mice, J. Pharmacol. & Exper. Therap. **106**:135-140, 1952.

161. Dougherty, T. F.: Effect of Hormones on Lymphatic Tissue, Physiol. Rev. **32**:379-401, 1952. Frank, J. A., and Dougherty, T. F.: Cytoplasmic Budding of Human Lymphocytes Produced by Cortisone and Hydrocortisone in in Vitro Preparations, Proc. Soc. Exper. Biol. & Med. **82**:17-19, 1953.

162. Hudson, G.; Herdan, G., and Yoffey, J. M.: Effect of Repeated Injections of ACTH upon the Bone Marrow, Brit. M. J. **1**:999-1002, 1952.

163. Burkell, C. C.: Radiation Leukopenia and Cortisone, J. Canad. A. Radiologists **3**:30, 1952.

164. Thiersch, J. B.; Conroy, L.; Stevens, A. R., and Finch, C. A.: Adverse Effect of Cortisone on Marrow Regeneration Following Irradiation, J. Lab. & Clin. Med. **40**:174-181, 1952.

165. Jacobson, B. M., and Sohier, W. D.: Effects of ACTH and of Cortisone on the Platelets in Idiopathic Thrombopenic Purpura, New England J. Med. **246**:247-249, 1952.

166. Stefanini, M.; Santiago, E. P.; Chatterjea, J. B.; Dameshek, W., and Salomon, L.: Corticotropin (ACTH) and Cortisone in Idiopathic Thrombocytopenia Purpura, J. A. M. A. **149**:647-653, 1952.

167. Studer V. A., and Frey, J. R.: Wirkung von Cortison auf die ruhende und die mit Vitamin A oder Testosteronpropionat zur Proliferation gebrachte Epidermis der Ratte, Dermatologica **104**:1-18, 1952.

in wound healing.[168] Thus, there may be a reduction in fibroplasia, decreased vascularization and capillary budding, and a reduction in exudation. Delayed wound healing following the clinical use of cortisone continues to be reported.[169] Moreover, its value in the prevention of adhesions or fibrous strictures appears to be quite definite in certain instances.[170] However, negative reports have appeared.[171] It has been shown, too, that wound healing is not appreciably retarded in experimental animals under cortisone therapy provided the animal is receiving an adequate diet, particularly of protein.[172] The over-all evidence would indicate that the hormones do not alter wound healing sufficiently to be of great clinical significance, and that when they do, both anti-inflammatory and general metabolic factors may be involved.

Specific studies, some during previous years, have permitted the same general conclusions with reference to wound healing of the eye. Epithelial healing of ocular structures is not greatly altered. Keratoblastic and fibroblastic response, however, may be inhibited. Subconjunctival injection of cortisone has been reported to delay healing of an experimental section in clear cornea.[173] On the other hand, such therapy was noted to have little effect upon the healing of lesions made at the limbus, although parenteral administration was found markedly to inhibit scleral healing.[174] The reason for this difference is not certain, and the problem must be considered to be unsettled at the moment.

Alteration of Inflammatory Response.—Cortisone profoundly alters the inflammatory response to many noxious agencies, e. g., thermal burns, chemical irritants, foreign protein, or bacteria. Histologically, the effect of cortisone appears to be a reduction in all elements of the inflammatory process, including leucocytic infiltration, transudation, capillary thrombosis, and hemorrhage.[175] The decreased leucocytic infiltration, in the face of the leucocytosis that may be caused by these hormones, must be interpreted as due to a diminished diapedesis through the vessel wall. The hormones delay phagocytosis, retard the clumping of foreign particles, and variably

168. Lattes, R.; Blunt, J. W.; Rose, H. M.; Jessar, R. A.; Vaillancourt, de G., and Ragan, C.: Lack of Cortisone Effect in the Early Stages of Inflammation and Repair, Am. J. Path. **29**:1-19, 1953. Spain, D. M., and Molomut, N.: Effect of Cortisone in Inflammation in Mice, Am. J. Clin. Path. **22**:944-947, 1952.

169. Rubin, A., and Lischner, M. D.: Effect of Premedication of Cortisone on the Healing of Wounds in an Infant, Connecticut M. J. **16**:682-683, 1952.

170. Baker, R.; Govan, D., and Huffer, J.: Inhibitory Effect of Cortisone on Strictures of the Urological Tract, Surg., Gynec. & Obst. **95**:446-454, 1952. Carstam, N.: Prevention of Experimental Tendon Adhesions by Cortisone, Acta orthop. scandinav. **22**:15-24, 1952.

171. Taylor, F. W.; Dittmer, T. L., and Porter, D. O.: Wound Healing and the Steroids, Surgery **31**:683-690, 1952.

172. Findlay, C. W., and Howes, E. L.: Combined Effect of Cortisone and Partial Protein Depletion on Wound Healing, New England J. Med. **246**:597-604, 1952.

173. James, W. M.; Power, J. L., and Ripple, P. H.: Experimental and Clinical Observations of the Effects of Cortisone in Corneal Lesions, Am. J. Ophth. **35**:1298-1304, 1952

174. Laval, J., and Coles, R. S.: Role of Cortisone in Glaucoma Surgery, A. M. A. Arch. of Ophth. **49**:168-181, 1953.

175. Moon, V. H., and Tershakovec, G. A.: Influence of Cortisone upon Acute Inflammation, Proc. Soc. Exper. Biol. & Med. **79**:63-65, 1952. Spain, D. M.; Molomut, N., and Haber, A.: Studies of the Cortisone Effects on the Inflammatory Response: I. Alterations of the Histopathology of Chemically Induced Inflammation, J. Lab. & Clin. Med. **39**:383-389, 1952.

delay fibrosis when foreign particles are introduced onto the peritoneum or into the bronchial tree.[176] Intravenously administered cortisone has been found to accumulate at the site of a chemically induced inflammation.[177]

Cortisone is known to inhibit hyaluronidase and decrease the permeability of inflamed capillaries. These actions may explain, at least in part, the anti-inflammatory action of the hormone. However, other factors are probably involved. These include a suppression of leucotaxine by cortisone [177] and an increased vascular tone.[178] For the most part, it is considered that the anti-inflammatory action of corticotropin is due to the cortisone or hydrocortisone released by the adrenal gland. However, it has been reported that chemically (formaldehyde) induced arthritis in adrenalectomized rats may be inhibited by the injection of corticotropin, as well as cortisone,[179] suggesting some effect of the pituitary hormone itself. This inhibitory effect of corticotropin was largely voided in the castrated-adrenalectomized animal.

The anti-inflammatory activity of cortisone and corticotropin is essentially the same in the eye as elsewhere. Important studies on the intraocular penetration of cortisone in experimental animals have indicated that topically applied cortisone enters the anterior chamber but that penetration into the vitreous is less marked.[180] Subconjunctival injection results in higher levels in both the aqueous and the vitreous. Penetration from the blood stream readily occurs. By any route, cortisone protects the rabbit eye against thermal, acid, and alkali burns of the cornea,[181] lessening the formation of scar tissue and corneal vascularization. Cortisone and corticotropin block the inflammatory response induced by injection of jequirity or Staphylococcus toxin into the eye.[182] There is a certain quantitation of effect, however, since high concentrations of the chemical irritant were capable of overcoming the protective effect. Local application of cortisone blocks the inflammatory response of cyclodiathermy and cycloelectrolysis.[183]

The alteration of the inflammatory tissue response to bacteria and other infectious elements which cortisone and corticotropin induce may have serious sequelae. Since the defense mechanisms are inhibited, the resistance to bacterial invasion is reduced. For example, fatal streptococcic bacteremia was observed in 71 of 76 rabbits treated with cortisone, whereas only 3 of the 86 nontreated animals died

176. Curran, R. C.: Effect of Cortisone on the Reaction of the Mouse Peritoneum to Quartz, Brit. J. Exper. Path. **33**:82-86, 1952. Harrison, C. V.; King, E. J.; Dale, J. C., and Sichel, R.: Effect of Cortisone on Experimental Silicosis, Brit. J. Indust. Med. **9**:165-172, 1952.

177. Menkin, V.: Localization of Cortisone in an Inflamed Area, Federation Proc. **11**:106, 1952.

178. Soskin, S.: Physiologic Basis for the Therapeutic Effects of Cortisone, Rev. Gastroenterol. **19**:808-816, 1952.

179. Gubner, R.; Cote, L.; Hughes, J.; Oleson, J. J.; Ruegsegger, J. M., and Williams, J. H.: Comparative Effects of Aminopterin, Cortisone and ACTH in Experimental Formaldehyde Arthritis and Psoriatic Arthritis, J. Invest. Dermat. **19**:297-305, 1952.

180. Leopold, I. H., and Maylath, F. R.: Intraocular Penetration of Cortisone and Its Effectiveness Against Experimental Corneal Burns, Am. J. Ophth. **35**:1125-1134, 1952

181. Leopold and Maylath.[180] Michaelson, I. C., and Haifa, I.: Effect of Cortisone upon Corneal Vascularization Produced Experimentally, A. M. A. Arch. Ophth. **47**:459-464, 1952.

182. Woods, A. C., and Wood, R. M.: Effect of Cortisone and ACTH on Ocular Inflammation Secondary to the Injection of Irritant Substances, Bull. Johns Hopkins Hosp. **90**:134-148, 1952.

183. Sheppard, L. B.: Comparative Effects of Cortisone on Rabbit Eyes Treated by Cyclodiathermy and Cyclo-Electrolysis, Am. J. Ophth. **36**:193-203, 1953.

of the infection.[184] In these studies the antistreptolysin titer developed at the same time and to the same degree in both the control and the cortisone-treated animals. Prior immunization, however, by living streptococci largely prevented the fatalities in the cortisone-treated group. A similar spread of experimental syphilis and other infections has been reported.[185] Indeed, the suggestion has been made that cortisone may be of value in determining the presence of reservoirs of infection or subclinical infections in animals.[186] The increased invasion of bacteria is probably due to a combined lack of fibrin barrier and decreased phagocytosis.[187]

The problem of dissemination of bacterial infection is perhaps most serious in tuberculosis.[188] In the tuberculous experimental animal under treatment with cortisone, a decrease in the lymphocytic infiltration and an increase in the number of bacilli has been observed.[189] The response seems to vary, however,[190] and in some experimental situations no harmful effect is observed. Cortisone does not appear to alter the response of experimental infections to streptomycin.[191] Study of the inflammatory response to tuberculous infection in the hypersensitive animal has been done in vivo, using the rabbit ear chamber technique.[192] In these studies cortisone was observed to check the inflammatory response, maintain better vascular tone, reduce the damage to arteriolar and venular endothelium, and decrease exudation and diapedesis of leucocytes. Interesting experiments on experimental ocular tuberculosis have been described.[193] Corticotropin, cortisone, and hydrocortisone (Compound F) did not control the inflammatory process or the development of tuberculous lesions in the nonimmune rabbit. On the other hand, when the injection was made into the eye of the immune-allergic rabbit, both cortisone and corticotropin blocked the focal reaction to the tuberculin in the inoculum and the early development of tuberculous lesions. Cortisone and corticotropin were

184. Mogabgab, W. J., and Thomas, L., Jr.: Effects of Cortisone on Bacterial Infections: Group A Hemolytic Streptococcal Infection in Rabbits, J. Lab. & Clin. Med. **39**:271-289, 1952.

185. DeLamater, E. D.; Saurino, V. R., and Urbach, F.: Studies on the Immunology of Spirochetoses: I. Effect of Cortisone on Experimental Spirochetosis, Am. J. Syph. **36**:127-139, 1952. Germuth, F. G., Jr.; Ottinger, B., and Oyama, J.: Influence of Cortisone on the Evolution of Acute Infection and the Development of Immunity, Bull. Johns Hopkins Hosp. **91**:22-48, 1952.

186. Antopol, W., and Quittner, H.: The Changing Pattern of Infectious Processes Under the Influence of Cortisone, J. Mt. Sinai Hosp. **19**:91-105, 1952.

187. Cook, C., and Smith, C.: Sepsis and Cortisone, Nature, London **170**:980, 1952.

188. Molomut, N., and Spain, D. M.: Effect of a Minimal Dose of Cortisone Combined with a Subeffective Dose of Dihydrostreptomycin on Experimental Guinea Pig Tuberculosis, Am. Rev. Tuberc. **67**:101-102, 1953.

189. Engbaek, H. C.; Friis, T., and Theilum, G.: Effect of Cortisone on the Tuberculous Infection in Mice and Guinea Pigs, Acta path. et microbiol. scandinav. **31**:317-324, 1952.

190. Cummings, M. M.; Hudgins, P. C.; Whorton, M. C., and Sheldon, W. H.: Influence of Cortisone and Streptomycin on Experimental Tuberculosis in the Albino Rats, Am. Rev. Tuberc. **65**:596-602, 1952. Winner, H. I., and Evans, W. E. D.: Experimental Tuberculosis in Cortisone-Treated Guinea Pigs, Tubercle **33**:239-242, 1952.

191. Bacos, J. M., and Smith, D. T.: Effect of Corticotropin (ACTH), Dihydrostreptomycin, and Corticotropin-Dihydrostreptomycin on Experimental Bovine Tuberculosis in the Rabbit, Am. Rev. Tuberc. **67**:201-211, 1953. Karlson, A. G., and Gainer, J. H.: Failure of Cortisone to Affect the Therapeutic Activity of Streptomycin in Experimental Tuberculosis of Guinea Pigs, Proc. Staff Meet., Mayo Clin. **27**:465-471, 1952.

192. Ebert, R. H.: In Vivo Observations on the Effect of Cortisone on Experimental Tuberculosis, Using the Rabbit Ear Chamber Technique, Am. Rev. Tuberc. **65**:64-74, 1952.

193. Woods, A. C., and Wood, R. M.: Studies in Experimental Ocular Tuberculosis, A. M. A. Arch. Ophth. **47**:477-512, 1952.

found to be more effective than hydrocortisone. With cessation of treatment, the animal showed a violent response, which has been termed "the rebound phenomenon" and has been suggested to be due to an overwhelming infection.

It is reasonably clear from these data that when one is considering the effect of cortisone on a bacterial infection at least three elements should be sharply delineated. The first is the inflammatory response to the bacteria as a foreign substance. This may be altered by cortisone to the extent that bacterial invasion is increased. The second is the development of immune bodies and the protection which immunity affords. This appears to be little altered by cortisone. The third is the inflammatory response of the tissue, which is hypersensitive to the bacteria or its products, e. g., tuberculin. This response is reduced by cortisone.

Lastly, experimental evidence favors the view that virus diseases, such as poliomyelitis, spread more rapidly and produce severer symptoms in the animals treated with cortisone or corticotropin.[194] Studies on herpes simplex of the eye have indicated that cortisone may cause release of the virus from the nuclei and permit the spread of infection.[195]

Alteration of Allergic Response.—Of particular interest is the study of allergy and the modification by corticotropin or cortisone of the reaction of the hypersensitive subject to the sensitizing agent. The field is somewhat confusing, however, owing to a rather loose use of terms and the propensity of workers to speak of many disease processes as allergic phenomena without adequate proof of hypersensitivity. Excellent reviews on the subject of allergy, including ocular allergy, have been published during the past year.[196]

Again, the distinction between immunity and hypersensitivity must be kept in mind. Often the same terms are used in describing the two conditions. The concern here is with the hypersensitivity response and the protective effect which cortisone affords. Attempts to analyze this protective effect have contributed the following information over the last several years and during the year under review: First, while the formation of antibodies may be inhibited to a certain extent,[197] this inhibition is undoubtedly not complete. Antibody formation may proceed during therapy with corticotropin and cortisone.[198] It is not intended to imply that the antibody measured here is the same as that which confers hypersensitivity. Rather,

194. Findlay, G. M., and Howard, E. M.: Effects of Cortisone and Adrenocorticotrophic Hormone on Poliomyelitis and on Other Virus Infections, J. Pharm. & Pharmacol, **4**:37-42, 1952. Shwartzman, G., and Fisher, A.: Alteration of Experimental Poliomyelitis Infection in the Syrian Hamster with the Aid of Cortisone, J. Exper. Med. **95**:347-362, 1952.

195. Braley, A. E.: Experimental Herpes Simplex, Am. J. Ophth. **35**:1737-1747, 1952.

196. Berens, C.; Sayad, W. Y., and Girard, L. J.: Symposium: Ocular Allergy: I. The Uveal Tract and Retina; Consideration of Certain Experimental and Clinical Concepts, Tr. Am. Acad. Ophth, **56**:220-241, 1952. Castroviejo, R.: Symposium: Ocular Allergy: II. Cornea and Lens, ibid. **56**:242, 1952. Hanser, S. A.: Symposium: Ocular Allergy: III. External Eye and Aqueous, ibid. **56**:256, 1952. Brown, E. A.: ACTH and Allergy, Ann. Allergy **10**:356-391, 1952. Evans, R. R., and Rackermann, F. M.: Allergy—Corticotropin and Cortisone, A. M. A. Arch. Int. Med. **90**:96-127, 1952.

197. Hayes, S. P., and Dougherty, T. F.: Effect of ACTH and Cortisone on Antibody Synthesis and Rate of Disappearance of Antigen, Federation Proc. **11**:67, 1952.

198. Clayton, B. E.; Hardisty, R. M., and Pinniger, J. L.: Studies on Antibody Formation to ACTH in Man, J. Endocrinol. **8**:56-63, 1952. Hunter, O. B., Jr., and Ross, J. B.: Cortisone in Rh Incompatibilities, South. M. J. **45**:732-738, 1952.

it is implied that the production of that substance which gives rise to the hypersensitive response is little altered by cortisone. (It is interesting that the transplantation of tumors, homologous as well as heterologous, is successful in the presence of cortisone therapy, suggesting that cortisone may inhibit antibody formation to the tissue transplant.[199]) Second, cortisone and corticotropin do not appear to inhibit the antigen-antibody reaction in the tissues. Thus, cortisone fails to protect against active or passive anaphylactic shock in experimental animals or to alter certain intradermal reactions.[200] Third, it seems reasonably well established that cortisone and corticotropin do not alter the reaction of tissue to histamine locally, although they may diminish the reactivity to histamine of tissues altered by allergic disease.[201] It is interesting that cortisone may protect against histamine in the adrenalectomized, but not in the intact, animal and that epinephrine potentiates this protection.[202]

The hypersensitivity responses which are altered by cortisone, hydrocortisone, and corticotropin include the tuberculin reaction, particularly in the more sensitive subjects.[203] In an interesting study,[204] it was demonstrated that a strongly positive Frei reaction could be inhibited by cortisone. When the drug was discontinued, the reaction again became positive. Yet, the complement-fixing titer of the patient's serum was not altered by the cortisone.

199. Agosin, M.; Christen, R.; Badinez, O.; Gasic, G.; Neghme, A.; Pizzaro, O., and Jarpa, A.: Cortisone-Induced Metastases of Adenocarcinoma in Mice, Proc. Soc. Exper. Biol. & Med. **80**:128-131, 1952. Foley, E. J.: Effect of Cortisone Acetate on Growth of Strain Specific Tumors in Alien Strains of Mice, ibid. **80**:669-671, 1952. Green, H. N., and Whiteley, H. J.: Cortisone and Tumor Growth, Brit. M. J. **2**:538-540, 1952.

200. Andersson, E.: Adrenocorticotropic Hormone (ACTH) and Cortisone: Their Effect on Intradermal Reactions, Acta allergol. **5**:58-71, 1952. Germuth, F. G., Jr.; Ottinger, B., and Oyama, J.: Influence of Cortisone on Experimental Hypersensitivity and Circulating Antibody in the Guinea Pig, Proc. Soc. Exper. Biol. & Med. **80**:188, 1952. Jeter, W. S., and Seebohm, P. M.: Effect of Cortisone and Adrenocorticotropic Hormone on Delayed Hypersensitivity to 2,4-Dinitrochlorobenzene in Guinea Pigs, ibid. **80**:694, 1952.

201. Grob, D.; Winkenwerder, W. L., and Schoenrich, E. H.: Effect of the Adrenocorticotropic Hormone (ACTH) Administration on Skin, Conjunctival and Nasal Mucous Membrane Reactivity to Histamine and Antigens in Man, Bull. Johns Hopkins Hosp. **90**:301-312, 1952.

202. Halpern, B. N.; Benacerraf, B., and Briot, M.: Role of Cortisone, Desoxycorticosterone and Adrenalin in Protecting Adrenalectomized Animals Against Hemorrhagic, Traumatic, and Histaminic Shock, Brit. J. Pharm. **7**:287-297, 1952; Potentiation by Adrenaline of Protective Effect of Cortisone on Histamine Toxicity in Adrenalectomized Mice, Proc. Soc. Exper. Biol. & Med. **79**:37-39, 1952.

203. Appel, S. B.; Fulton, L. A., and Orr, K. D.: Observations on Essentially Normal Young Men Treated with ACTH and Cortisone: II. Effects on Tuberculin, Dick, and Shick Tests, U. S. Armed Forces M. J. **3**:373-384, 1952. Goldman, L.; Thompson, R. G., and Trice, E. R.: Cortisone Acetate in Skin Disease: Local Effect in the Skin from Topical Application and Local Injection, A. M. A. Arch. Dermat. & Syph. **65**:177-186, 1952. Goldman, L.; Preston, R. H.; Rockwell, E., and Baskett, J.: Inhibition of Tuberculin Reaction by Local Injection of Compound F, J. A. M. A. **150**:30-31, 1952. Leahy, R. H., and Morgan, H. R.: Inhibition by Cortisone of the Cytotoxic Activity of PPD on Tuberculin-Hypersensitive Cells in Tissue Culture, J. Exper. Med. **96**:549, 1952. Pyke, D. A., and Scadding, J. G.: Effects of Cortisone Upon Skin Sensitivity to Tuberculin in Sarcoidosis, Brit. M. J. **2**:1126-1128, 1952.

204. Grace, A. W.; Frank, L., and Wyse, R. J.: Effect of Cortisone Upon Hypersensitivity Due to Lymphogranuloma Venereum, A. M. A. Arch. Dermat & Syph. **65**:348-350, 1952.

An attempt to summarize this rather confusing field has been published during the past year.[205] The author points out that there are, in general, two types of allergic responses, an immediate and a delayed, and that the two differ in their histopathology. He suggests that cortisone is relatively ineffective against the immediate allergic response, i. e., those reactions in which preformed histamine-like substances are released, as occurs from pollen sensitivity. This sensitivity can be passively transferred via the serum. On the other hand, the delayed response is greatly altered by the anti-inflammatory hormones. Examples of this type of response are the tuberculin reaction and the contact dermatitides. This type of sensitivity is not transferable, and thus the antibody is thought to reside within, or be firmly attached to, the cell. The delayed response, he argues, is due to the fact that the inflammatory substance is not preformed but is manufactured after the antigen-antibody reaction. This substance is probably a leucotaxine, a polypeptide apparently formed by the action of a protease. There are thought to be many leucotaxines. This accounts for the different cellular responses. According to this concept, cortisone and hydrocortisone inhibit either the production of this inflammatory substance or its action. As has already been pointed out, cortisone inhibits leucotaxine.[177] Certain support for this approach is gained from the observation that inhibition by cortisone and corticotropin of a skin reaction to an antigen in sensitive cattle does not occur until some hours after injection of the inhibitor.[206] Immediate protection is afforded by an antihistaminic.

The concept has admitted inadequacies, but serves as a point of departure for consideration of the clinical use of these drugs in allergic states.

Preparations Available.—Corticotropin is available for intramuscular and intravenous use. The potency of the various preparations is standardized in terms of biologic effectiveness. Extremely potent extracts may be prepared.[207] Clinically, the greatest effectiveness from the use of corticotropin is achieved by continuous intravenous administration. The clinically optimal amount to be given over any given period is 20 international units (equivalent to 20 mg. of the Armour standard).[208] The recommended period is eight hours. Rapid intravenous injection of this amount has no biologic effect. Intramuscular absorption is less certain, partly because of the variable purity of the product. Cases of resistance to corticotropin are probably explained on this basis. Recently, several long-acting preparations of the hormone for intramuscular use have been developed. The clinical effectiveness of these products is said to be good.[209]

205. Pickering, G. W.: Allergy and A. C. T. H., Brit. M. J. **1**:1207-1210, 1952.

206. Kerr, W. R., and Robertson, M.: Effect of ACTH, Cortisone, Sphingomyelin, Sphingosine and Phanergan (Antihistamine) in Inhibiting the Skin Reaction in Cattle Sensitized to Trichomonas Foetus Antigen, J. Hyg. **50**:354, 1952.

207. Raben, M. S.; Rosenberg, I. N.; Westermeyer, V. W., and Astwood, E. B.: Enhanced Clinical Effectiveness of Purified Corticotropin, J. A. M. A. **148**:844-845, 1952.

208. Renold, A. E.; Jenkins, D.; Forsham, P. H., and Thorn, G. W.: Intravenous ACTH: A Study in Quantitative Adrenocortical Stimulation, J. Clin. Endocrinol. **12**:763, 1952.

209. Bruce, H. M., and Parkes, A. S.: A Slow-Release Medium for Adrenocorticotropic Hormone, Lancet **1**:71-72, 1952. Lamar, C. P.: Experiences with the Therapeutic Use of a Long-Acting Corticotrophic Preparation, J. Florida M. A. **39**:167-173, 1952. Wolfson, W. Q., and Fajans, S. S.: A Comparison of the Duration of Action of Various Long-Acting ACTH Preparations in Human Subjects, New England J. Med. **246**:1000-1004, 1952.

There appears to be no good evidence that corticotropin has any notable superiority over cortisone or hydrocortisone in clinical effectiveness. The intravenous use of corticotropin may be advisable in those cases in which one wishes to be certain of a maximum clinical effect.

Both cortisone and hydrocortisone are now available for both systemic and local use. Cortisone is marketed as the acetate for local, oral, and parenteral use. Hydrocortisone presently is marketed as the free alcohol for oral use and as the acetate for local use in the eye and for intra-articular injection.

There is little doubt that hydrocortisone is more effective biologically, gram for gram, than is cortisone, as determined by such indices as the degree of eosinopenia and glucosuria. Its anti-inflammatory effects seem, likewise, to be greater than those of cortisone. Whether it will prove to have any merit over cortisone in equivalent clinical dosage remains to be seen. Orally, the free alcohol of hydrocortisone has been found to be more effective, milligram for milligram, than either its acetate or the free alcohol or acetate of cortisone.[210] Hydrocortisone acetate has been found to be more effective than cortisone acetate used locally in arthritic joints and on the skin.[211] Reports of the use of hydrocortisone acetate in the eye have been limited, but indicate that it may possibly be more effective topically than is cortisone acetate.[212] One of the intriguing questions of the clinical use of cortisone is the reason for its more effective local action in the eye than elsewhere in the body. The reason is still obscure. Whether the free alcohol of hydrocortisone will prove to be more effective locally than the acetate remains to be ascertained. The effectiveness of the free alcohol on the skin has been reported to be less than that of its acetate ester.

Use in Ocular Disease.—The use of corticotropin and the corticosteroids, particularly cortisone, in the treatment of various ocular diseases and disorders has been widely reviewed in the ophthalmologic literature.[213] In general, it has been

210. Boland, E. W.: Antirheumatic Effects of Hydrocortisone (Free Alcohol), Hydrocortisone Acetate, and Cortisone (Free Alcohol) as Compared with Cortisone Acetate, Brit. M. J. **1**:559-564, 1952. Boland, E. W.: Rheumatoid Arthritis—Experiences with Hydrocortisone (Free Alcohol) and Hydrocortisone Acetate, California Med. **77**:1-6, 1952.

211. Bilka, P. J.: Intra-Articular Use of Hydrocortisone in Rheumatic Diseases, Minnesota Med. **35**:938-943, 1952. Goldman, L.: Local Effect of Compound F on Reactions to Mosquito Bites, J. A. M. A. **149**:265, 1952. Sulzberger, M. B., and Witten, V. H.: Effect of Topically Applied Compound F in Selected Dermatoses, J. Invest. Dermat. **19**:101-102, 1952. Ziff, M.; Scull, E.; Ford, D.; McEwen, C., and Bunim, J. J.: Effects in Rheumatoid Arthritis of Hydrocortisone and Cortisone Injected Intra-Articularly, A. M. A. Arch. Int. Med. **90**:774-784, 1952.

212. Steffensen, E. H.; Ivy, H. B., and Nagle, F. O.: Topical Compound F in the Treatment of Anterior Segment Eye Disease, Am. J. Ophth. **35**:933-934, 1952. Steffensen, E. H.: Corticotropin, Cortisone and Hydrocortisone in Treatment of Ocular Disease, J. A. M. A. **150**:1660-1664 1952.

213. Abel, H.: Topical Cortisone in Eye Disease, Acta ophth. **30**:45-52, 1952. Bissell, G. W.: New Concepts in the Use of ACTH in Ophthalmology and Otolaryngology, Tr. Am. Acad. Ophth. **56**:450-456, 1952. Fine, M., and Goodwin, R. C.: Evaluation of Local Cortisone Therapy in Ophthalmology, A. M. A. Arch. Ophth. **47**:787-797, 1952. Franceschetti, A.; Maeder, G., and Bourquin, J. B.: La cortisone en ophtalmologie (observations expérimentales et cliniques), Ann. ocul. **185**:36-65, 1952. François, J.: La cortisone en ophtalmologie, ibid. **185**:401-413, 1952. Irvine, S. R.: ACTH and Cortisone in Ophthalmology, Ann. West. Med. & Surg. **6**:438-440, 1952. Minnes, J. F.: Topical Cortisone in Eye Diseases, Canad, M. A. J. **66**:342-347,

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concluded that, when beneficial, topical application of cortisone acetate is usually effective in conditions involving the anterior segment. Parenteral administration is recommended for involvement of the posterior segment and for those disease processes of the anterior segment which do not respond to topical application of cortisone when such response might be expected.

In an excellent review, Woods cites his previous conclusions concerning the clinical usefulness of corticotropin and cortisone in diseases of the eye as follows:[214]

(a) In certain inflammatory conditions of the eye, especially those affecting the cornea, uveal tract, and external eye, the parenteral administration of ACTH or cortisone, or the topical administration of cortisone, is followed in a high percentage of cases by a dramatic control of the inflammatory and exudative phases of disease. These agents do not affect the cause of the disease but rather influence the reaction of tissues to the cause or to the irritant.

(b) In many diseases favourably influenced there is a definite tendency for the inflammation to recur after cessation of treatment.

(c) In certain oedematous and inflammatory conditions, especially secondary glaucoma, inflammations of the retina and optic nerve, and oedematous corneal grafts, and also probably in syphilitic interstitial keratitis, the action of cortisone and ACTH is variable and cannot be accurately predicted.

(d) In some haemorrhagic and exudative conditions (Coats's disease, Eales's disease, malignant exophthalmos, diabetic retinopathy and retrolental fibroplasia) no consistent therapeutic results have as yet been demonstrated.

(e) In degenerative disease, whether of the cornea, retina, or uveal tract, these agents are totally ineffective.

Very little has been added in the past year which would tend to negate or qualify those conclusions. Among the reports of interest are those which tend to show quite conclusively that retrolental fibroplasia does not respond to corticotropin or cortisone therapy.[215] This treatment has proved ineffective in Sjögren's syndrome.[216] A study of its effect on scleromalacia perforans demonstrated that while cortisone may reduce the inflammatory response, it may also inhibit the regenerative process if the cortisone concentration is too high.[217] Experimental studies with cortisone and antibiotics have indicated that the combination of antibiotic and

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1952. Ormsby, H. L.; Shirley, S. Y.; Aikenhead, J. F., and Murray, R. G.: ACTH and Cortisone Therapy in Eye Disease, ibid. **66**:62-66, 1952. Rouher, F.: Comment et quand utiliser la cortisone en ophtalmologie, Presse méd. **60**:784-786, 1952. Salomaa, S., and Swanljung, H.: Clinical Experiences with ACTH and Cortisone in Eye Diseases, Acta ophth. **30**:53-61, 1952. Thorpe, H. E.: Use of Cortisone and ACTH in Eye Diseases, Pennsylvania M. J. **55**:236-240, 1952.

214. Woods, A. C.: Uses and Limitations of ACTH and Cortisone in Ophthalmology, Brit. J. Ophth. **36**:401-431, 1952.

215. LaMotte, W. O., Jr.; Tyner, G. S., and Scheie, H. G.: Treatment of Retrolental Fibroplasia with Vitamin E, Corticotropin (ACTH) and Cortisone, A. M. A. Arch. Ophth. **47**:556-569, 1952. Reese, A. B.; Blodi, F. C.; Locke, J. C.; Silverman, W. A., and Day, R. L.: Results of Use of Corticotropin (ACTH) in Treatment of Retrolental Fibroplasia, ibid. **47**:551-555, 1952.

216. Cadman, E. F. B., and Robertson, A. J.: Treatment of Sjögren's Syndrome with A. C. T. H., Brit. M. J. **2**:68-70, 1952. Sjögren, H., and Eriksen, A.: ACTH and Keratoconjunctivitis Sicca, Acta ophth. **30**:463-465, 1952.

217. Ashton, N., and Hobbs, H. E.: Effect of Cortisone on Rheumatoid Nodules of the Sclera (Scleromalacia Perforans), Brit. J. Ophth. **36**:373-384, 1952.

cortisone may have value in the treatment of infectious processes.[218] Cortisone therapy may be of value in sarcoidosis,[219] although recurrence after treatment is the rule. It appears to control interstitial keratitis.[220] Certain other reports on the effect of cortisone on the eye and certain of its diseases are listed.[221]

In summary, then, from what is known of the effect of cortisone and hydrocortisone on the tissues in general and the eye in particular, the use of these hormones, either locally or systemically, would be calculated to be successful primarily where one wishes to block an inflammatory response induced by a noxious agent, such as physical trauma, bacteria, chemical irritants, foreign protein, or some substance to which the patient may be hypersensitive. The particular structures of the eye which seem to be most responsive to this inhibitory effect on the inflammatory process are the uveal tract, the external coats, the conjunctiva, and the skin of the lids. They protect the cornea from some of the ravages of an inflammatory process. Both vascularization and scarring are reduced. Use of these hormones in infectious processes may be beneficial provided the infectious element can be controlled by chemotherapy. They may successfully control certain allergic responses, such as nongranulomatous uveitis and certain manifestations of the external eye. They are not curative.

Use in General Medicine.—The clinical use of cortisone and corticotropin and their effectiveness in the treatment of other conditions of medical interest follow a similar pattern. Thus, they continue to be used in rheumatic fever [222] and rheu-

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matoid arthritis.[223] Their use, with varying success, in acute disseminated lupus erythematosus, polyarteritis nodosa, pemphigus, scleroderma, and erythema nodosum has been reported.[224] Their value in certain allergic skin manifestations, such as contact dermatitis, appears likely.[225] Certain blood dyscrasias and bleeding diatheses, including the acute leukemias, chronic lymphocytic leukemia, certain hemolytic anemias, and in certain cases, agranulocytosis and aplastic anemia respond variously.[226] Finally, cortisone is used as replacement therapy for adrenal insuffi-

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ciency. The hormone may be of value in this regard in certain debilitating illnesses in which adrenal exhaustion might reasonably have occurred.[227]

Complications Resulting from Therapeutic Use.—Despite the fact that the administration of these hormones may produce a variety of unwanted hormonal effects, such as moon face, reduced glucose tolerance, hypertension, acne, hirsutism, edema, and psychic changes, there are relatively few contraindications to the hormone therapy, since these effects on the whole disappear shortly after treatment is discontinued. The use of these hormones is contraindicated in hypertension in the presence of renal insufficiency. Tuberculosis or arrested tuberculosis is not necessarily an absolute contraindication, although exacerbations certainly may occur.[228] A peptic ulcer may flare up during corticotropin or cortisone therapy, with fatal sequelae.[229] Rigorous management with antacid therapy of healing, or even healed, ulcers appears advisable. Perforation of the bowel during treatment of ulcerative colitis has been reported.[230] The diabetogenic effect of the hormones has been mentioned. Osteoporosis and pathologic fracture may follow prolonged treatment with corticotropin or corticosteroids.[231] The thyroid status appears to be of little importance, although thyroiditis developing during cortisone therapy has been reported.[232] Psychotic disturbances may, on occasion, reach serious proportions. Cortisone appears to increase the excitability of nerve tissue, as measured by the electroshock seizure threshold. Desoxycorticosterone has the opposite effect.[233] The hyperexcitability can be counteracted to a certain extent with phenobarbital and diphenylhydantoin.

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NONHORMONAL AGENTS USED IN SIMILAR DISORDERS

The merit of the corticosteroids and corticotropin in the treatment of rheumatic fever and rheumatoid arthritis led to a reevaluation of the role of action of salicylates. There is certain evidence that the salicylates may act in some manner on the pituitary-adrenal axis and that their effect may be due, at least in part, to a release of corticosteroid.[234] Clinical features suggestive of adrenocortical excess have been observed in patients being treated with salicylates.[235] Certain differences and antagonistic effects of cortisone and salicylates, however, are described.[236] The ability of salicylates to inhibit fibrinolysin may enhance their anti-inflammatory effects.[237]

Phenylbutazone has been used with some success in rheumatic disorders.[238] It is stated, however, to have only an analgesic and antipyretic, rather than any true antirheumatic, effect.[239] The drug is not without toxicity, a variety of side-effects, including agranulocytosis, having been reported.[240] An interesting side-effect of the drug has been the observed reduction in radioactive-iodine uptake by the thyroid gland.[241]

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Finally, the question of fever therapy and its possible therapeutic mechanism has been of interest. Among the agents used for induction of such fever are typhoid vaccine and the bacterial pyrogens. The latter are polysaccharides derived from bacteria, which on injection produce a rise in temperature and an increase in the white cell count.[242] The mode of action of fever therapy is not certain. Most likely, the release of corticosteroids is stimulated in some manner. These fever-inducing drugs find use in ocular and other diseases.[243] The comparative role of the pyrogens and cortisone in ophthalmology needs further evaluation.

AUTONOMIC DRUGS

Cholinergic and Parasympathomimetic Drugs

In general, it is well to adhere to that terminology which classifies cholinergic agents as those which, like acetylcholine, directly stimulate the effector organ innervated by the parasympathetic system, e. g., the iris sphincter and the ciliary muscle. Parasympathomimetic agents have no direct stimulatory action but permit the accumulation of the acetylcholine normally released at the nerve endings of the parasympathetic system. These substances are the anticholinesterases. The cholinergic agents act on peripherally denervated structures, whereas the parasympathomimetic drugs do not.

Because of its instability, acetylcholine is more a laboratory oddity than a therapeutic agent. It mediates the transmission of the nerve impulse across synapses of the central nervous system, the myoneural junctions, all autonomic ganglia, and the postganglionic endings of the parasympathetic nervous system. Action at the autonomic ganglia or myoneural junctions is spoken of as a nicotinic effect of the compound, while stimulation of the parasympathetic postganglionic nerve endings is known as a muscarinic effect. The ciliary ganglion is similar to other autonomic ganglia in its response to acetylcholine and ganglion-blocking agents.[244] The most frequently used cholinergic drugs are methacholine (acetyl-β-methylcholine; Mecholyl), carbachol (carbaminoylcholine; Doryl), and pilocarpine. The first two are closely related to acetylcholine chemically, while pilocarpine differs widely. Of these compounds, acetyl-β-methylcholine has little nicotinic action, its action being predominantly muscarinic. It is readily hydrolyzed by cholinesterase. Carbachol has a more pronounced nicotinic action and is only slowly hydrolyzed by cholinesterase. Pilocarpine has only muscarinic action and is not altered by the cholinesterases. Little new has been reported on the use of these drugs in the past year.

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Acetylcholine is rapidly hydrolyzed by the enzyme cholinesterase. There are two types of cholinesterases, a true, or specific, type and a pseudo type. The latter is a nonspecific esterase, which hydrolyzes acetylcholine more slowly than does the true cholinesterase. Acetyl-β-methylcholine is hydrolyzed only by the true cholinesterase and may be used as substrate when a measure of the activity of the latter enzyme is desired. The cholinesterase found in ocular structures, including the iris sphincter and ciliary muscle, is chiefly the specific type.[245] The cholinesterase content of the iris of the cat falls to about 40% of the normal level after removal of the ciliary ganglion.[246]

There are two types of cholinesterase inhibitors, those which temporarily inhibit the activity of the enzyme (physostigmine and neostigmine) and those which permanently destroy it (diisopropyl fluorophosphate). They attach to different portions of the enzyme. The attachment of the first type is reversible and is gradually broken as these inhibitors are either destroyed or excreted. (Physostigmine and neostigmine are enzymatically destroyed in human serum, probably by plasma cholinesterase.[247]) Studies with diisopropyl fluorophosphate containing radioactive phosphorus have demonstrated that this drug introduces a phosphate radical into the cholinesterase, and probably in this manner permanently inhibits enzyme activity.[248]

Both the therapeutic and the toxic effects of these inhibitors result from the accumulation of acetylcholine, which is thus protected from hydrolysis. Of the two groups, the phosphate-containing inhibitors are the most potent. In addition to diisopropyl fluorophosphate, those of medical interest are octamethylpyrophosphoramide, tetraethylpyrophosphate, hexaethyltetraphosphate and diethyl-*p*-nitrophenylthiophosphate (Parathion). The phosphate inhibitors are very toxic and may be absorbed by the skin in sufficient quantity to be fatal. A comparative study of the oral toxicity of these phosphorus-containing inhibitors indicates that, on a gram-for-gram basis, tetraethylpyrophosphate is the most toxic in experimental animals.[249] Some of these substances are used as insecticides and may be the cause of accidental human poisoning.[250] Atropine is the antidote and may be required in high dosage.

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The use of various anticholinesterase drugs in ophthalmology has recently been evaluated.[251] Physostigmine, diisopropyl fluorophosphate, and tetraethylpyrophosphate were found to produce more rapid miosis than neostigmine and benzpyrinium (Stigmonene) bromide. Diisopropyl fluorophosphate gave the most prolonged miosis. This drug in relatively dilute solution, 0.01%, has been reported to control the intraocular pressure in mild, chronic wide-angle glaucoma.[252] The use of diisopropyl fluorophosphate to counteract partially the cycloplegic action of atropine has been suggested.[253] Hazards of the use of diisopropyl fluorophosphate in the eye continue to be reported, including the precipitation of an acute glaucomatous attack in narrow-angle glaucoma [254] and a possible causal relation between the instillation of diisopropyl fluorophosphate in an aphakic eye and the development of retinal detachment.[255]

The other use of these drugs of interest here is in the treatment of myasthenia gravis. The exact cause of this disorder is uncertain,[256] although a curare-like substance in the blood stream of affected patients has been demonstrated.[257] The diagnostic use of curare or neostigmine in suspected cases of myasthenia gravis is well known. A new anticurare drug, edrophonium (Tensilon) chloride, may be the drug of choice for this purpose.[258] This compound is chemically similar to neostigmine but less potent than the latter drug as a cholinesterase inhibitor. The muscarinic side-effects of edrophonium are thus less than those of neostigmine. Neostigmine is generally the drug of choice in the treatment of myasthenia gravis.[259] Octamethylpyrophosphoramide may have certain therapeutic advantages.[260] This compound apparently has no activity of its own but is converted, presumably by the liver, into an unidentified cholinesterase inhibitor.

Parasympathetic-Blocking Agents

The parasympathetic-blocking agents block the response of the effector cell to the direct-acting drugs and to nerve stimulation. Their use in ophthalmology

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centers around their iridoplegic and cycloplegic effects. Certain newer agents, known as 75 G. T. (Cyclogyl) 92 G. T. and 93 G. T., appear to have distinct advantages as cycloplegics.[261] These compounds, particularly 93 G. T., approach atropine in their effectiveness. The cycloplegia they induce persists for less than a day. No local or systemic toxic effects have been noted. Methantheline (Banthine) bromide, a drug which is widely used as an antispasmodic, has been reported to be a valuable cycloplegic for infants and preschool children.[262] Employed as a 4% ointment, no gastrointestinal side-reactions, local irritations, or sensitivities were observed. A 2% aqueous solution of methantheline bromide, on the other hand, was found to be irritating and not highly effective as a cycloplegic.[261a] A mixture of 5% phenylephrine (Neo-synephrine) hydrochloride and 5% eucatropine (Euphthalamine) in methylcellulose has been recommended as a mydriatic for the examination of premature infants.[263]

The parasympathetic-blocking agents are mainly used in medicine for their gastrointestinal effects.[264] The major problem here is to find an agent which has maximum antispasmodic activity but minimal activity elsewhere, as in the eye. Thus, specific point has been made of the fact that a parasympathetic-blocking agent, dicylomine (Bentyl) hydrochloride, used for such purposes, did not interfere with the control of glaucoma.[265] Such emphasis is probably unnecessary, since in general the systemic use of these agents in a patient with coexistent glaucoma has presented no problem. Compounds of this group reported to have minimal ocular activity are diphenmethanil (Prantal) methylsulfate and scopolamine-*n*-bromobutylate (SKF-1637).[266] A number of other parasympathetic-blocking agents have been synthesized, but their clinical value, particularly in ophthalmology, remains to be determined.[267] Attention has been directed to the fact that the parasympathetic-

261. (*a*) Gettes, B. C., and Leopold, I. H.: Evaluation of 5 New Cycloplegic Drugs, A. M. A. Arch. Ophth. **49**:24-27, 1953. (*b*) Stolzer, I. H.: A New Group of Cycloplegic Drugs, Am. J. Ophth. **36**:110-112, 1953.

262. Raiford, M. B.: Use of Banthine in Ophthalmology, South. M. J. **45**:633-636, 1952.

263. Reiter, C.: A New Synergistic Mydriatic Combination, Am. J. Ophth. **35**:412-413, 1952.

264. Liebowitz, D.; Raisin, A.; Berry, C., and Roth, H. P.: Treatment of Intractable Peptic Ulcer with Methantheline (Banthine) Bromide, J. A. M. A. **150**:672-677, 1952. Steinberg, N.: New Anticholinergic Drugs in Peptic Ulcer Therapy, Rev. Gastroenterol. **19**:351-370, 1952.

265. Hufford, A. R.: Bentyl Hydrochloride: Successful Administration of a Parasympatholytic Anti-Spasmodic in Glaucoma Patients, Am. J. Digest. Dis. **19**:257-258, 1952.

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267. Biel, J. H.; Friedman, H. L.; Leiser, H. A., and Sprengeler, E. P.: Antispasmodics: Substituted Acetic Acid Esters of 1-Alkyl-3-Hydroxypiperidine, J. Am. Chem. Soc. **74**:1485-1488, 1952. Cheney, L. C.; Wheatley, W. B.; Specter, M. E.; Byrd, W. M.; Fitzgibbon, W. E.; Minor, W. F., and Binkley, S. B.: Basic Amides as Antispasmodic Agents: I, J. Organic Chem. **17**:770-777, 1952. Moffett, R. B., and Hunter, J. H.: Antispasmodics: Mono- and Dimethyltyrrolidylalkyl Esters of Disubstituted Acetic Acids, J. Am. Chem. Soc. **74**:1710-1712, 1952. Ruddy, A. W., and Bishop, H. W.: Antispasmodics: *N*-Methyl-2(4)-(W-R-W-Phenylalkyl)-Piperidines and 2-R-2-Phenyl-4(5)-(*N*-Methyl-4-Piperidyl)-Alkanenitriles, J. Am. Chem. Soc. **74**:1919-1921, 1952.

and certain sympathetic-blocking agents reduce perspiration and, particularly in hot weather, may cause hyperthermia and heat stroke.[268]

Adrenergic and Sympathomimetic Drugs

The terminology here follows the pattern discussed under the parasympathetic agents. Adrenergic drugs directly stimulate the cells innervated by the sympathetic nervous system. Those drugs which have no direct stimulating effect but which block the destruction of locally released sympathin are spoken of as sympathomimetic agents.

Evidence favors the view that l-arterenol (nor-epinephrine) is the substance released at the postganglionic endings of the sympathetic nervous system. Epinephrine, in smaller amounts, may be released as well.[269] Epinephrine, however, is the compound released in greatest quantity by the adrenal medulla,[270] although arterenol can be identified in adrenal extracts and in accessory chromaffin tissue in the body.[271] The two are very similar chemically. Arterenol is probably the precursor of epinephrine. Injected into the blood stream, arterenol has a potent vasoconstrictive and pressor effect, whereas epinephrine may be either a vasodilator or a vasoconstrictor, depending upon the dose and the site and duration of action.

As in the parasympathetic system, there is an enzyme (amine oxidase) present in close proximity to the sympathetic nerve endings which inactivates sympathin. This enzyme has been identified in the iris and the nictitating membrane of experimental animals.[272] Amine oxidase destroys arterenol more rapidly than epinephrine,[273] a property which perhaps accounts for the fact that, of the two, epinephrine is the more powerful mydriatic. After denervation of the iris, the enzyme activity is reduced, and the mydriasis produced by the two drugs is essentially the same. It has been suggested that the signs of sympathetic activity seen in hyperthyroidism are due to a decrease in concentration of amine oxidase. Epinephrine is also oxidized by the DOPA-oxidase system of pigmented ocular tissues, whereas arterenol is not.[274] It has been suggested that this activity of the pigmented tissue accounts for the known fact that brown irides respond to mydriatics more poorly than blue.

A number of adrenergic agents are available on the market. These are generally similar chemically to epinephrine, although some are aliphatic amines. Cocaine is considered to be a sympathomimetic agent. Some drugs, such as ephedrine, have both adrenergic and sympathomimetic activity.

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268. Litman, R. E.: Heat Sensitivity to Autonomic Drugs, J. A. M. A. **149**:635-636, 1952.

269. Outschoorn, A. S.: The Nature of Sympathin Released in the Rabbit's Ear, Brit. J. Pharmacol. **7**:616-624, 1952.

270. Swan, H. J. C.: Noradrenaline, Adrenaline and the Human Circulation, Brit. M. J. **1**:1003-1006, 1952.

271. Shepherd, D. M., and West, G. B.: Noradrenaline and Accessory Chromaffin Tissue, Nature, London **170**:42-43, 1952.

272. Robinson, J.: Amine Oxidase in the Iris and Nictitating Membrane of the Cat and the Rabbit, Brit. J. Pharmacol. **7**:99-102, 1952.

273. Burn, J. H.: The Enzyme at Sympathetic Nerve Endings, Brit. M. J. **1**:784-787, 1952.

274. Angenent, W. J., and Koelle, G. B.: Destruction of Epinephrine by the DOPA-Oxidase System of Ocular Tissue, Science **116**:543-544, 1952.

These drugs are used in ophthalmology largely for their mydriatic and decongestive effects. Epinephrine has only moderate action on the iris dilator when instilled into the conjunctival sac, perhaps because it is so readily destroyed by amine oxidase. It is commonly used, therefore, in conjunction with cocaine when a strong mydriatic effect is desired. Those agents which are not so readily oxidized by the enzyme system, such as hydroxyamphetamine (Paredrine) and phenylephrine hydrochloride, may be preferred for routine mydriasis. Differences in penetrability may also be important. The administration of phenylephrine in ointment base (methylcellulose) rather than in aqueous solution has been advocated.[275] Hydroxyamphetamine in weak solution (0.1%) is recommended as a vasoconstrictive agent in chronic conjunctivitis, particularly in older persons.[276] In this concentration it appears to have no mydriatic action. A host of other sympathetic amines are available for local use. The usefulness of arterenol clinically in the field of ophthalmology has not been fully explored. Its main advantage over epinephrine would be its powerful vasoconstrictor action.

Elsewhere in medicine, these agents are used largely for their pressor and decongestive actions. Arterenol is a valuable drug for the treatment of hypotension or profound shock.[277] It is feasible to maintain a severely hypotensive patient for several days by its intravenous use. Tissue necrosis following subcutaneous infiltration with arterenol has been reported.[278] This may have been the result of a profound local vasoconstriction. Epinephrine injection causes eosinopenia, and the eosinopenic response to this drug has been considered a measure of the integrity of the pituitary-adrenal axis. The validity of this concept, however, has been questioned.[279] Amphetamine has been shown of definite value in barbiturate poisoning.[280] Newer agents with pressor or vasoconstrictive effects have been reported,[281] as the search continues for drugs which have a powerful vasoconstrictive effect but do not alter cardiac rhythm or otherwise exhibit adverse side-effects.

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275. Bedrossian, R. H., and Deichler, J. W.: Phenylephrine (Neo-Synephrine) Ointment, A. M. A. Arch. Ophth. **48**:747-748, 1952.

276. Lipsius, E. I.: Paredrine Hydrobromide in Chronic Conjunctivitis, Am. J. Ophth. **35**:1692-1695, 1952.

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279. Muehrcke, R. C.; Staple, T. W., and Kark, R. M.: Epinephrine Eosinopenia in Surgically Induced Addison's Disease, J. Lab. & Clin. Med. **40**:169-173, 1952.

280. Dick, H. L.: Use of Amphetamine in Barbiturate Poisoning, Am. J. M. Sc. **224**:281-285, 1952.

281. Brofman, B. L.: Hellerstein, H. K., and Caskey, W. M.: Mephentermine—An Effective Pressor Amine, Am. Heart J. **44**:396-406, 1952. Nathanson, M. H., and Miller, H.: Clinical Observations on a New Epinephrine-like Compound, Methoxamine, Am. J. M. Sc. **223**:270-279, 1952. Sutton, B. M., and Data, J. B.: Vasoconstrictors: 2-Amino Derivatives of Certain Alkoxyalkanes, J. Am. Pharm. A. (Scient. Ed.) **41**:328-332, 1952. Taylor, G. W.: Clinical Evaluation of Armine, a New Sympathomimetic Amine, A. M. A. Arch. Otolaryng. **56**:213-214, 1952.

Adrenergic and Sympathetic-Blocking Agents

An acceptable terminology of these drugs is as follows: Adrenergic-blocking agents, or adrenolytic substances, block the effect of epinephrine on the cells. Those drugs which block the response to stimulation of the sympathetic nerves are called sympathetic-blocking agents, or sympatholytic substances. A further distinction between lytic and blocking agents is sometimes made but will not be used here. Drugs which block the autonomic ganglia are sympatholytic (as well as parasympatholytic), whereas drugs which act peripherally may be both sympatholytic and adrenolytic.

Of the peripheral blocking agents, the earliest used were the alkaloids of ergot. These have a sympatholytic and an adrenolytic action, of varying degrees. A mixture of certain of the hydrogenated ergot alkaloids, dihydroergocristine, dihydroergocornine, and dihydroergokryptine (known as Hydergine) appears to block vasospastic activity peripherally. Dihydroergokryptine reduces cerebral vascular tone in experimental animals, although its action here may not be sympatholytic.[282] Other ergot derivatives, such as ergotamine tartrate, are known to be effective agents in the treatment of migraine.[283] This action of ergot drugs does not appear to be due to sympathetic blockade.

In recent years, several other compounds which have a peripheral blocking action have been developed. Among these are the benzodioxane derivatives, such as 933 F, the substituted haloethylamines, of which the best-known example is Dibenamine (*N*,*N*-dibenzyl-β-chloroethylamine hydrochloride), and certain imidazoline derivatives, such as tolazoline (Priscoline). They have sympatholytic and adrenolytic activity, of varying degrees.[284] Not all compounds necessarily have both. The hyperglycemia (glycogenolysis) which epinephrine induces is also blocked by these agents, but there appears to be little correlation between the antihyperglycemic and the antipressor effects of these drugs.[285] The ethylamine group is a relatively constant feature of antihistaminics and the β-haloethylamines have some antihistaminic activity.[286] Tolazoline is excreted unchanged in the urine, its biologic half-life being approximately two hours.[287] The fate of the other agents is not established.

The use of these peripheral sympathetic-blocking agents in ophthalmologic practice has been limited. Dibenamine is of value in treatment in certain cases of acute glaucoma that is unresponsive to other medications. The ocular hypotensive action

282. Taeschler, M.; Cerletti, A., and Rothlin, E.: Zur Frage der Hyderginwirkung auf die Gehirnzirkulation, Helvet. physiol. et pharmacol. acta **10**:120-137, 1952.

283. Fuchs, M., and Blumenthal, L. S.: Use of Ergot Drugs for Migraine, M. Ann. District of Columbia **21**:372-375, 1952.

284. Polonovski, M.; Schmitt, H., and Pelou, A.: Activité adrénolytique et sympatholytique d'un dérivé, la *N*-phenoxyisopropyl-*N*-benzyl-β-chloroéthylamine, Compt. rend. Soc. biol. **146**: 1560-1563, 1952.

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286. Graham, J. D. P., and Lewis, G. P.: Relationship Between Anti-Adrenaline and Anti-Histamine Activity in a Series of β-Haloethylamines, J. Physiol. **116**:37P-38P, 1952.

287. Brodie, B. B.; Aronow, L., and Axelrod, J.: Fate of Benzazoline (Priscoline) in Dog and Man and a Method for Its Estimation in Biological Material, J. Pharmacol. & Exper. Therap. **106**:200-207, 1952.

of the β-haloethylamine derivatives is not fully understood, although there are indications that these drugs block secretory activity in aqueous formation.[288] The dihydrogenated alkaloids of ergot have been reported to reduce spasm of the retinal arterioles.[289] Tolazoline, administered both orally and intravenously, has been reported to be of value in retinal angiospasm and certain ocular diseases in which a vasodilator might be of some value.[290] An interesting study employing angioscotometry has indicated that when exudation is a feature of diabetic retinopathy the retinal vessels do not respond to tolazoline.[291] The clinical significance of this is not certain.

Among the clinical uses of these agents in other fields of medicine has been that of the benzodioxane derivatives and Dibenamine in the diagnosis of pheochromocytoma.[292] Tolazoline and the dihydrogenated ergot alkaloids may be of value in the treatment of certain peripheral vascular disorders.[293] These agents are of little value in the treatment of hypertension.[294]

Ganglion-Blocking Agents

Ganglioplegic agents are mostly used clinically for their sympatholytic effect. It is to be remembered, however, that these agents also block the ganglia of the parasympathetic system including the ciliary ganglion, and, in certain instances, e. g., for the reduction of gastric acidity, may be employed clinically for this purpose. The classic ganglion-blocking agent is nicotine. This substance stimulates the autonomic ganglia in low concentrations but is paralytic if the concentration is raised. It has no clinical value.

There are two main groups of compounds used clinically. Both are quaternary ammonium bases. The first group includes tetramethylammonium and tetraethylammonium halide. The latter is known as Etamon. The main action of these com-

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289. Gibbs, D. F.: Dihydrogenated Alkaloids of Ergot in the Investigation and Treatment of Diastolic Hypertension, Brit. Heart J. **14**:77-86, 1952.

290. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Response of the Retinal Vessels to Priscoline in Various Vascular Conditions: Study I., Am. J. Ophth. **35**:191-195, 1952. Stern, J. J.: A New Vasodilator in Ophthalmology, ibid. **35**:187-190, 1952.

291. Cholst, M. R.; Schilback, H. F.; Handelsman, M. B., and Levitt, L. M.: Response of the Retinal Vessels into Priscoline Diabetes Mellitus: Study II., Am. J. Ophth. **35**:375-380, 1952.

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293. Hurley, L. A., and Buchanan, A. R.: Prophylactic and Therapeutic Value of Hydergine in High Altitude Frostbite, Surg., Gynec. & Obst. **95**:423-430, 1952. Mufson, I.; Goldman, L.; Hirschman, S.; Sheiman, M.; Blier, J., and Steinberg, G.: An Evaluation of Priscoline by Artery in the Treatment of Peripheral Arterial Obliterativve Disease, New York J. Med. **52**:2651-2654, 1952. Roberts, J. E.; Anderson, L. L., and Parry, T. M.: Clinical Effectiveness of Certain of the Hydrogenated Alkaloids of Ergot in Peripheral Vascular Disorders, Am. J. M. Sc. **224**:431-438, 1952.

294. Bakke, J. L., and Williams, R. H.: Treatment of Essential Hypertension with β-Alkylamines, Especially Dibenzyline, Am. J. Med. **14**:141-159, 1953. Elek, S. R.; McNair, J. D., and Griffith, G. C.: Clinical Comparison of 2 Hypotensive Drugs: Newer Ergot and Veratrum Alkaloids, Am. Pract. & Digest Treat. **3**:693-696, 1952. Ertwisle, G., and Stone, C. A.: Effect of Prolonged Administration of Adrenergic Blocking Drug on Blood Pressure of Hypertensive Dogs, Am. J. Physiol. **172**:245-250, 1953. Sutton, G. C.; Buckingham, W.; Brown, R. D., and Sutton, D. C.: A Clinical Evaluation of the Treatment of Hypertension with Dihydrogenated Ergotoxine Alkaloids, Am. Heart J. **44**:622-628, 1952.

pounds is ganglioplegic, although they have a certain curare-like effect.[295] The methonium compounds constitute the other group.[296] These consist of tetramethyl ammonium groups, separated by a variable number of carbon atoms. They have both ganglioplegic and curariform activity. Of these compounds, the five and six carbon lengths, i. e., pentamethonium and hexamethonium, are potent ganglion-blocking agents, whereas the longer compounds, particularly decamethonium (10 carbon atoms), block the myoneural junction preferentially. Hexamethonium is the compound most frequently used for ganglion-blocking activity and is effective perenterally, as well as orally.

Administration of these agents is followed by a profound hypotension, and direct evidence of sympathetic blockade can be demonstrated.[297] At the same time, the parasympathetic system is blocked, and intestinal paresis and obstruction may result from overdosage or extreme sensitivity to the drugs.[298] These compounds are excreted via the kidney practically unchanged, and a vicious cycle may result in those extreme cases in which the blood pressure falls so markedly that glomerular filtration is diminished. A case of unilateral amaurosis apparently resulting from extreme hypotension during use of the drug in general surgery has been reported.[299]

The application of these agents to ophthalmology has been limited. As a result of the action of these drugs, the pupil may become moderately dilated and unresponsive to light and in accommodation. Blurring of vision, due to paralysis of accommodation, may also occur. Hexamethonium lowers both the normal and the elevated ocular tension.[300] This effect appears to be due to the fall in blood pressure, although, certainly, this cannot be asserted with any finality. The value of these agents in the treatment of glaucoma remains to be determined. Because of its profound effect on the blood pressure, hexamethonium gives a "bloodless" field and has found widespread use in general surgery.[301] It has been suggested that both the reduced bleeding and the ocular hypotension which result from the use of this compound make it of value in intraocular surgery.[302]

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295. Atkinson, W. J., Jr.: Effect of Tetraethylammonium Chloride on Mammalian Skeletal Muscle Action, Am. J. Physiol. **168**:442-445, 1952.

296. Paton, W. D. M., and Zaimis, E. J.: The Methonium Compounds, Pharmacol. Rev. **4**:219-253, 1952.

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298. Goldstone, B.: Death Associated with Methonium Treatment, South African M. J. **26**:552-554, 1952. Finnegan, T. R. L., and Trounce, J. R.: Intolerance to Hexamethonium Bromide, Brit. M. J. **2**:75-76, 1952.

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301. Gillies, J.: Physiological Trespass in Anesthesia, Proc. Roy. Soc. Med. **45**:1-6, 1952. Kenney, S.: Controlled Hypotension, Irish J. M. Sc. **6**:241-253, 1952.

302. Hill, K. R., and Goodwin, G. P.: Influence of Hypotension on the Intracapsular Cataract Operation, Brit. J. Ophth. **36**:683-688, 1952. Rycroft, B. W., and Romanes, G. J.: Preliminary Report on the Use of Methonium Compounds and General Anaesthesia in Ophthalmic Surgery, ibid. **36**:29-36, 1952.

Aside from their use in surgery, these drugs are mostly prescribed at present for the treatment of arterial hypertension, i. e., for the production of medical sympathectomy.[303] Hexamethonium is the ganglioplegic agent most frequently employed. Two other drugs, hydralazine (1-hydrazinophthalazine; Apresoline)[304] and the alkaloids of Veratrum viride[305] are also used in the treatment of hypertension. The manner in which the latter drugs reduce the blood pressure is not known with certainty. They do not fall into any of the above classifications. Various combinations of hexamethonium and hydralazine appear also to have value.[306] Only cautious claims of benefit are made at present. The merit of a particular drug may depend upon the cause of the hypertension. The results show some promise in treatment of malignant hypertension. Hypertensive retinopathy may respond. Among the other uses of these drugs have been that of hexamethonium in the treatment of hyperhidrosis[307] and of tetraethylammonium chloride for the relief of the spasm of coronary artery disease.[308]

(A word about the cation-exchange resins and similar compounds would not be amiss at this point, since these agents are used in the treatment of hypertension, as well as other conditions in which depletion of sodium chloride is desired. Taken orally, these compounds bind the sodium in the gastrointestinal tract and prevent

303. Davies, G.; Wales, B. A.; Paterson, A. S., and Oxon, M. A.: Use of "Etamon" for High Blood-Pressure in Electrocerebral Treatment, J. Ment. Sc. **98**:306-308, 1952. Johnson, I.; Moyer, J. H.; Mills, L. C., and Miller, S. I.: Treatment of Hypertension: Results with Hexamethonium Salts Administered Orally, Texas J. Med. **48**:331-334, 1952. McMichael, J.: Management of Hypertension, Brit. M. J. **1**:933-938, 1952. McQueen, E. G.: Treatment of Hypertension with Hexamethonium Bromide, M. J. Australia **2**:425-428, 1952. Palmer, A. J.: Management of Hypertension with Hexamethonium Bromide, ibid. **2**:428-435, 1952. Robinson, C. M.: The Methonium Compounds and Their Use in the Treatment of Hypertension, J. Bowman Gray School Med. **10**:87-95, 1952. Shaw, G. B.: Continuous Oral Hexamethonium in Essential Hypertension: Further Experiences in Treatment, Glasgow M. J. **33**:410-420, 1952.

304. Khan, M. A.: Effect of Hydralazine in Hypertension, Brit. M. J. **1**:27-29, 1953. Riven, S. S., and others: Control of Hypertension with 1-Hydrazinophthalazine (Apresoline), Am. J. Med. **14**:160, 1953.

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306. Grimson, K. S.; Orgain, E. S.; Rowe, C. R., and Sieber, H. A.: Caution with Regard to Use of Hexamethonium and "Apresoline," J. A. M. A. **149**:215-220, 1952. Johnson, R. L.; Freis, E. D., and Schnaper, H. W.: Clinical Evaluation of 1-Hydrazinophthalazine (C-5968) in Hypertension with Special Reference to Alternating Treatment with Hexamethonium, Circulation **5**:833-841, 1952. Schroeder, H. A.: Control of Hypertension by Hexamethonium and 1-Hydrazinophthalazine, A. M. A. Arch. Int. Med. **89**:523-540, 1952.

307. Sommerville, J., and MacMillan, J. B.: Treatment of Essential Hyperidrosis with Hexamethonium Bromide: A Preliminary Report, Brit. J. Dermat. **64**:442-446, 1952.

308. Hirshleifer, I.; Schwartz, G.; Fuerst, H. J., and Fankhauser, A.: Tetraethylammonium Chloride in the Treatment of Coronary Artery Disease, New York J. Med. **52**:575-579, 1952.

its absorption.[309] They appear to be very effective. Indeed, a serious sodium depletion may occur. A hypopotassemia may also result, and, for this reason, potassium supplements must be given. While the accumulation of sodium chloride, which occurs with the administration of corticotropin and cortisone, can be prevented to a certain extent by simultaneous use of the cation-exchange resins, patients so treated exhibit a severe hypopotassemia even if potassium supplements are given. Hence use of the resins in cortisone therapy is not recommended.[310])

MUSCLE RELAXANTS

The use of curare-like agents in both intraocular and strabismus surgery continues to be advocated.[311] As a generalization, the ganglioplegic and the curariform drugs may be said to differ only in the comparative degree to which they paralyze the autonomic ganglia and the myoneural junction. The curariform drugs have certain chemical similarities, i. e., two quaternary ammonium groups separated by a rather crucial distance.

In general, two groups of agents have been recognized. Included in the first of these are the so-called true curare agents, such as curare, tubocurarine, U. S. P., and gallamine (Flaxedil). These agents apparently block the action of acetylcholine on the muscle receptor, probably by virtue of a competitive action. They may also inhibit acetylcholine production at the myoneural junction.[312] This group has a more pronounced ganglioplegic action and causes a greater release of histamine than does the other group.[313] Their action is blocked, at least in part, by such agents as neostigmine and edrophonium.[314] With all compounds maximum therapeutic effect is reached in about 20 minutes and wears off in about 40 minutes. Intramuscular injection of tubocurarine gives more prolonged relaxation.[315]

309. Aaron, R. S., and Weston, R. E.: Outpatient Treatment of Congestive Heart Failure with Sodium-Removing Exchange Resins, A. M. A. Arch. Int. Med. **90**:182-195, 1952. Best, M. M.: Use of an Anion-Cation Exchange Resin in Edematous States Contraindicating Mercurial Diuretics, Am. Pract. & Digest Treat. **3**:274-279, 1952. Gill, R. J., and Duncan, G. G.: Clinical Use of Alginic Acid as a Cation Exchanger, Am. J. M. Sc. **224**:569-572, 1952; Arterial Hypertension—the Therapeutic Effect of Cation-Exchange Resins, New England J. Med. **247**:271-276, 1952. Whiting, W. B., and Miller, M. S.: Cation Exchange Resins, Texas J. Med. **48**:585-590, 1952.

310. Bonner, C. D.: Electrolyte-Balance Studies in Normal Volunteers and Clinical Observations on the Effects of Cation-Exchange Resins in Patients with Cardiovascular Disease and in Subjects Receiving Pituitary Adrenocorticotropic Hormone (ACTH), New England J. Med. **247**:158-163, 1952. Greenman, L.; Weigland, F. A., and Danowski, T. S.: Cation Exchange Resin Therapy in Patients Receiving Cortisone or ACTH, Am. J. M. Sc. **225**:1-7, 1953.

311. Agarwal, L. P., and Mathur, S. P.: Curare in Ocular Surgery: Report of 25 Cases, Brit. J. Ophth. **36**:603-610, 1952. Thomas, K. B.: D-Tubocurarine Chloride in Strabismus Operations in Children, Anæsthesia **7**:97-98, 1952.

312. Naess, K.: The Mechanism of Action of Curare, Acta pharmacol. et toxicol. **8**:149-163, 1952.

313. Sniper, W.: Estimation and Comparison of Histamine Release by Muscle Relaxants in Man, Brit. J. Anæsth. **24**:232-237, 1952.

314. Doughty, A. G., and Wylie, W. D.: Antidotes to "True" Curarizing Agents, Including a Report on Ro 2-3198 (Tensilon), Brit. J. Anæsth. **24**:66-80, 1952. Hunter, A. R.: Tensilon: A New Anti-Curare Agent, ibid. **24**:175-186, 1952. Smith, C. M.; Cohen, H. L.; Pelikan, E. W., and Unna, K. R.: Mode of Action of Antagonists to Curare, J. Pharmacol. & Exper. Therap. **105**:391-399, 1952.

315. Fuller, J. D.: Advantages of the Preoperative Use of Slowly Absorbed D-Tubocurarine, Anesthesiology **13**:370-375, 1952.

The second group of curarizing agents are those which have the depolarizing action of an excess of acetylcholine. The muscle poisoned with these agents will not respond to an electric shock, whereas the muscle preparation poisoned with curare or tubocurarine will contract if electrically stimulated. Included in this group are such agents as decamethonium iodide and succinylcholine.[316] In general, these compounds do not have the profound autonomic-blocking action of the first group. Moreover, neostigmine and edrophonium have no antidotal action against this group of drugs. Certain agents which block tubocurarine actually enhance the curare effect of succinylcholine.[317] Succinylcholine is hydrolyzed by both the true cholinesterases and the pseudocholinesterases [318] and is the only one of the curariform drugs so altered. The others are excreted unchanged. Because of its hydrolysis, succinylcholine is short-acting. In addition, it produces paralysis very quickly. This combination of rapid onset and short period of activity makes succinylcholine a particularly valuable drug when muscle relaxation is desired.[319] Continuous intravenous administration may be required. That there is no antidote to this drug (except cholinesterase) is not too serious, since respiratory arrest will be relieved spontaneously as the succinylcholine is hydrolyzed. Use of any of these agents, however, requires a thorough knowledge of their action and adequate facilities for handling any untoward response.[320] The use of various of these synthetic muscle relaxants has been recently reviewed.[321]

There is one other group of agents which are interesting as muscle relaxants. These are the ethers of glycerol, of which the methylphenoxy ether, mephenesin (Myanesin; Tolserol), is the most widely used. It appears to be the most potent

316. Adamson, D. C., and Kinsman, F. M.: Succinyl Choline Chloride in Anaesthesia, Anæsthesia **7**:166-168, 1952. Churchill-Davidson, H. C., and Richardson, A. T.: Decamethonium Iodide (C 10): Some Observations on Its Action Using Electromyography, Proc. Roy. Soc. Med. **45**:179-186, 1952. Hall, L. W.; Lehmann, H., and Silk, E.: Response in Dogs to Relaxants Derived from Succinic Acid and Choline, Brit. M. J. **1**:134-136, 1953. Mayrhofer, O. K.: Self-Experiments with Succinylcholine Chloride, ibid. **1**:1332-1334, 1952. Mesham, P. R., and Barton, J. D. M.: A Report on Succinylcholine Chloride (Scoline): An Ultra-Short-Acting Muscle Relaxant, South African M. J. **26**:727-728, 1952. Thesleff, S.: Pharmacological Properties of Succinylcholine Iodide: With Particular Reference to Its Clinical Use as a Muscular Relaxant, Acta physiol. scandinav. **26**:103-129, 1952; An Investigation of the Muscle-Relaxing Action of Succinyl-Choline-Iodide in Man, ibid. **25**:348-367, 1952; An Investigation of Succinyl-Choline-Iodide in Man, ibid. **25**:368-376, 1952.

317. Phillips, A. P.: Dicarboxylic Acid bis-β-Tertiaryaminoalkyl Amides and Their Quaternary Ammonium Salts and Curare Substitutes: III. J. Am. Chem. Soc. **74**:4320-4321, 1952.

318. Evans, F. T.; Gray, P. W. S.; Lehmann, H., and Silk, E.: Effect of Pseudo-Cholinesterase Level on Action of Succinylcholine in Man, Brit. M. J. **1**:136-138, 1953. Whittaker, V. P., and Wijesundera, S.: Hydrolysis of Succinyldicholine by Cholinesterase, Biochem. J. **52**:475-479, 1952.

319. von Dardel, O., and Thesleff, S.: Succinylcholine Iodide as a Muscular Relaxant: A Report of 500 Surgical Cases, Acta chir. scandinav. **103**:321-336, 1952. Thesleff, S., and Holmberg, G.: Succinylcholine Iodide: A New Muscular Relaxant, Brit. J. Anæsth. **24**:238-244, 1952.

320. Vetten, K. B.; Nicholson, J. C., and Devitt, D. C.: Safety in the Use of Muscular Relaxants, South African M. J. **26**:814-817, 1952.

321. Foldes, F. F.; Machaj, T. S.; Hunt, R. D.; McNall, P. G., and Carberry, P. C.: Synthetic Muscle Relaxants in Anesthesia, J. A. M. A. **150**:1559-1566, 1952.

of all its isomers in its ability to relax spasm and antagonize the rigidity caused by tetanus toxin.[322] The drug has a weak curare-like effect.[323] However, in the usual clinical dose its main action is at the level of the spinal cord and the brain stem, where it reduces facilitation and inhibits multisynaptic reflexes.[324] In a higher dose it has a central depressant effect. It is used clinically to reduce muscle spasm arising from local irritation or other causes, such as multiple sclerosis and cerebral palsy.[325] The drug is short-acting clinically, and the dose must be repeated at relatively frequent intervals.

HISTAMINE AND ANTIHISTAMINES

While histamine is rather ubiquitous in the body, it has no proved function in the checks and balances that represent the normal physiologic state. It has, however, profound effects when injected or directly applied to certain tissues.[326] First, it induces a contraction of smooth muscle, e. g., that of the bronchial tree. Second, it causes vasodilatation, increases capillary permeability, and in some manner stimulates the endothelial cells of the blood vessels and capillaries to phagocytic action. Third, it has a stimulatory effect upon certain glandular tissues, such as the salivary and lacrimal glands and the adrenal medulla. When histamine is administered, the adrenal medulla releases a pressor substance into the blood stream, even though its autonomic innervation has been blocked.[327] Lastly, histamine stimulates the gastric mucosa.

Except as a diagnostic agent, the clinical value of histamine is equivocal. It is used diagnostically to stimulate the gastric mucosa and the adrenal medulla. Therapeutically, histamine has been employed intra-arterially and intravenously as a vasodilator.[328] It is reported to be of benefit in histamine cephalalgia and Ménière's disease.[329] It has also been suggested for the treatment of Bell's palsy; episcleritis, by local instillation; retrobulbar neuritis, and in certain cases of paralysis of the extraocular muscles attributed to vasospasm.[330]

The antihistamines are a group of compounds whose major therapeutic function is to block the action of histamine. In addition, they have certain side-effects which

322. Berger, F. M.: Central Depressant and Anticonvulsant Properties of Glycerol Ethers Isomeric with Mephenesin, J. Pharmacol. & Exper. Therap. **105**:450-457, 1952.

323. Davis, H.; Hine, C. H.; Neal, M. W.; Christensen, H. E., and Murphy, F. J.: Some Pharmacologic Comparisons of 1-Ethoxy- 3-Isopropoxypropane-2-ol and 3-(2-Methylphenoxy)-Propane-1,2-Diol (Myanesin), Arch. internat. pharamcodyn. **89**:145-159, 1952.

324. Taverner, D.: Action of α-β-Dihydroxy-γ-(2-Methylphenoxy)-Propane (Myanesin) on the Spinal Cord of the Cat, Brit. J. Pharmacol. **7**:655-664, 1952.

325. Album, M. M.: Dental Use of Mephenesin in Cerebral Palsy Patients: A Preliminary Report, J. Am. Dent. A. **45**:165-170, 1952. Libet, B., and Rubin, D.: Mephenesin in the Treatment of Spasticity in Multiple Sclerosis, J. Nerv. & Ment. Dis. **116**:198-209, 1952.

326. Loew, E. R.: Pharmacological Properties of Antihistaminics in Relation to Allergic and Nonallergic Disease, Boston M. Quart. **3**:1-6, 1952.

327. Slater, I. H., and Dresel, P. E.: Pressor Effect of Histamine After Autonomic Ganglionic Blockade, J. Pharmacol. & Exper. Therap. **105**:101-107, 1952.

328. Flanders, J. F.; Heckler, G. B., and Jones, R. E.: Intra-Arterial Histamine in Peripheral Vascular Disease, Delaware M. J. **24**:17-21, 1952. Furmanski, A. R.: Histamine Therapy in Acute Ischemia of the Brain, A. M. A. Arch. Neurol. & Psychiat. **69**:104-117, 1953.

329. Prewitt, L. H.: Histamine in the Practice of Otolaryngology, Tr. Am. Acad. Ophth. **56**:280-282, 1952. Schmidt, A.: A Review of Histamine and Its Clinical Use, J. Missouri M. A. **49**:235-243, 1952.

330. Skinner, D. A.: Histamine in Bell's Palsy, Tr. Am. Acad. Ophth. **56**:283-286, 1952.

have therapeutic value. Chemically, the antihistamines have certain similarities. Most have an aminoethyl group in common. A table of the comparative chemical compositions of many of these agents is to be found in a paper on the fungistatic activity of the antihistamines.[331] Their antihistaminic action can be demonstrated in many ways. They block the contraction of smooth muscle induced by histamine and protect against experimental anaphylactic shock. Their ability to block the effect of histamine on skin capillaries can be demonstrated.[332]

The antihistamines have other effects not attributable directly to the blocking of histamine. In relatively high concentration they have an atropine-like action. They have a local anesthetic potency, which may be greater than that of procaine, but they diffuse poorly in tissues.[333] They depress the response of skeletal muscle to electric stimulation, but this effect is seen only at higher tissue levels than would be achieved clinically.[334] They cause a limited central depression. Diphenhydramine (Benadryl) has been reported to be of value in relief of "thalamic pain."[335] Their effect on the eye, other than that of blocking histamine, appears to be explained, at least in part, by the atropine-like properties of the agent. Thus, in a case of diphenhydramine intoxication the pupils were found to be dilated and fixed.[336] The pupillary response in experimental animals is not constant. In some animals the pupil may be dilated but retain its ability to respond to light; in others a biphasic response may occur, dilatation followed by constriction.

The antihistamines are of proved merit in those instances in which the release of histamine or histamine-like substances is the cause of an untoward response. According to the reasoning indicated in the section on cortisone, this is the immediate, rather than the delayed, response. In the field of ophthalmology, as in dermatology,[337] the frequency of their local use appears to be diminishing. Their local use in certain allergic manifestations, such as allergic conjunctivitis, allergic episcleritis, and blepharoconjunctivitis, has been reported during the year under review.[338] There is commercially available for local use a solution containing two antibiotics, antihistamine and a decongestant. Favorable results from its use in the treatment of external disease have been reported.[339] The antihistamines may cause a contact dermatitis.

331. Mitchell, R. B.; Arnold, A. C., and Chinn, H. I.: Fungistatic Activity of Antihistamines, J. Am. Pharm. A. (Scient. Ed.) **41**:472-475, 1952.

332. Fabinyi-Szebehely, M., and Szebehely, J.: Influence of Antihistamines on the Effect of Histamine upon Body Temperature and Oxygen Consumption in Mice and Rats, Acta physiol. scandinav. **27**:1-9, 1952.

333. Kopel, D.: Comparison of the Anaesthetic Effects of Antihistamine and Local Anaesthetic Drugs of the Skin, Dermatologica **104**:408-414, 1952.

334. Murray, J. R., and Houston, M. J.: Effect of Diphenhydramine Hydrochloride (Benadryl HCl) on Skeletal Muscle, Arch. internat. pharmcodyn. **89**:204-208, 1952.

335. Barris, R. W.: Use of Benadryl for Symptomatic Relief of "Thalamic Pain," Neurology **2**:59-64, 1952.

336. Guard, H. L.: Benadryl Intoxication: A Case Report, M. Bull. European Command **9**:17-20, 1952.

337. Ellis, F. A., and Bundick, W. R.: Appraisal of Topical Use of Antihistamines, J. A. M. A. **150**:773-776, 1952.

338. Hurwitz, P.: Prophenpyridamine Maleate (Trimeton Maleate) in Ocular Allergy, Eye, Ear, Nose & Throat Month. **31**:251-254, 1952.

339. Hurwitz, P.: Drilitol in External Ocular Diseases, Am. J. Ophth. **35**:1134-1138, 1952.

Of the uses of the antihistamines in other fields of medicine, their value in anaphylactic reaction and in urticarial reactions due to drug sensitivities has been mentioned. They may relieve a histamine headache.[340] Their local use as an antipruritic, either by topical application or by iontophoresis, may be successful.[341] They probably are of little value in the treatment of the common cold or as an antitussive.[342] The value of diphenhydramine and its 8-chlorotheophyllin salt, dimenhydrinate (Dramamine), and of certain other antihistaminics in the control of postoperative nausea and motion sickness is well documented.[343] The antihistaminics also may be of definite benefit in Parkinson's disease.[344]

ENZYMES

Hyaluronidase

Hyaluronic acid, a mucopolysaccharide, is one of the normal constituents of the ground substance. It is found in relative abundance in the vitreous humor, synovial fluid, and umbilical cord. The mucoid substance in the cornea appears to be the sulfate of hyaluronic acid. Studies on the permeability of a connective tissue membrane and its alteration by hyaluronidase have indicated that hyaluronic acid may form a "waterproof" coating on the fibrillar elements of the connective tissue meshwork, fill the interfibrillar spaces, and thus inhibit the diffusion of fluids.[345] Hyaluronic acid has been shown to inactivate vaccine virus.[346] Thus, hyaluronic acid may serve as both a mechanical and a sterilizing barrier to the spread of infectious processes.

Hyaluronidase, the spreading factor, is the specific enzyme which hydrolyzes hyaluronic acid. Injection of the enzyme breaks down to a certain extent the tissue barriers to diffusion. More rapid and widespread dissemination of injected fluid and particles is thus permitted. The enhancing effect of the enzyme on the action of local anesthetics results from the readier penetrability of the anesthetic through the connective tissue and nerve sheath. The enzyme has no action on the nerve

340. Tucker, W. I., and O'Neill, P. B.: Benadryl in Histamine Headache, Lahey Clin. Bull. **7**:218-221, 1952.

341. Finkler, R. S.: Topical Antihistamine Therapy in Ano-Genital Pruritis, J. M. Soc. New Jersey **49**:264-265, 1952. Inman, P.; Cowan, I., and Campbell, C.: Antihistamine in Non-Urticarial Dermatoses and Retrial of Antihistamine Iontophoresis, Brit. M. J. **1**:1064-1066, 1952.

342. Boyd, E. M.: Cough Medication and Antihistaminic Drugs, Canad. M. A. J. **67**:289-292, 1952.

343. Chinn, H. I.; Handford, S. W.; Cone, T. E.; and Smith, P. K.: Effectiveness of Various Drugs for the Prophylaxis of Seasickness, Am. J. Med. **12**:433-439, 1952. Chinn, H. I., and Milch, L. J.: Comparison of Airsickness Preventives, J. Appl. Physiol. **5**:162-164, 1952. Moore, D. C.; Anderson, LeG.; Wheeler, G., and Scheidt, J.: Use of Parenteral Dramamine to Control Postoperative Vomiting: A Report of 1,192 Cases, Anesthesiology **13**:354-360, 1952.

344. Cohen, S. G., and Criep, L. H.: Observations on the Use of Antihistaminics in Parkinson's Disease (Paralysis Agitans), J. Nerv. & Ment. Dis. **115**:57-63, 1952

345. Day, T. D.: Permeability of Interstitial Connective Tissue and the Nature of the Interfibrillary Substance, J. Physiol. **117**:1-8, 1952.

346. Duran-Reynals, F., and Duran-Reynals, M. L.: Inactivation of Vaccine Virus by Preparations of Hyaluronic Acid With or Without Hyaluronidase: Experiments on Cell Cultures, Science **115**:40-41, 1952.

itself.[347] The edema of experimental cold injury is more rapidly reduced when hyaluronidase is used.[348] Hyaluronidase is reported to promote the phagocytosis of bacteria in vitro.[349]

In the field of ophthalmology, the use of hyaluronidase with injectable local anesthetics has been reported to give good results.[350] The enzyme has been stated to be of value in the treatment of pterygiums that have not advanced more than 1 mm. into the cornea and subconjunctival hemorrhage and to have been of benefit in a case of degenerative keratitis.[351] Hyaluronidase should not be used intraocularly. It has probably no merit in the treatment of exophthalmos.

In other fields of medicine, the enzyme is used to promote the spread of local anesthetics and the absorption of subcutaneously administered fluids or other substances.[352] An interesting use has developed in the field of urology.[353] When hyaluronidase is injected, the hydrolyzed molecules of hyaluronic acid are excreted into the urine, where they serve as a protective colloid and reduce the incidence of renal lithiasis.

Hyaluronidase is found in the streptococci and is considered to have some role in the pathogenicity of this organism.[354] The human subject forms an antihyaluronidase to the specific enzyme found in the Streptococcus with which he is infected.[355] A nonspecific hyaluronidase inhibitor is found in human blood and has been obtained in relatively pure form.[356] It appears to contain a certain amount of heparin. The liver may be a major source of production of this antihyaluronidase.[357] In certain diseases, such as rheumatic fever, the antihyaluronidase titer of the serum may rise.[358] Certain derivatives of gentisic acid, a possible end-product of salicylic

347. Nordqvist, P.: Action of Hyaluronidase on Frog Sciatic Nerve, with Special Reference to Penetration of Procaine, Acta pharmacol. et toxicol. **8**:195-206, 1952.

348. Pirozynski, W. J., and Webster, D. R.: Effect of Hyaluronidase on Edema Following Experimental Cold Injury, Proc. Soc. Exper. Biol. & Med. **80**:306-308, 1952.

349. Ludany, G.; Orban, T., and Vajda, G.: Hyaluronidase und die Bakterienphagozytose der Leukozyten, Arch. internat. pharmacodyn. **88**:490-501, 1952.

350. Tassman, I. S.: Use of Hyaluronidase in Ophthalmology, Am. J. Ophth. **35**:683-686, 1952.

351. Carriker, F. R.: Use of Hyaluronidase in Ophthalmology, Am. J. Ophth. **35**:1765-1768, 1952.

352. Astley, R.: Use of Hyaluronidase in Paediatric Urography, J. Fac. Radiologists **3**:280, 1952. Thale, H. B.: Use of Lyophilized Hyaluronidase in Cosmetic Surgery About Face, Plast. & Reconstruct. Surg. **10**:260-263, 1952. Webb, W. R.: Effect of Hyaluronidase on Rate of Absorption of Subcutaneous Fluids, A. M. A. Arch. Surg. **65**:770-773, 1952.

353. Butt, A. J.; Hauser, E. A., and Seifter, J.: Effect of Hyaluronidase on Urine and Its Possible Significance in Renal Lithiasis, J. A. M. A. **150**:1096-1098, 1952. Butt, A. J.; Seifter, J., and Hauser, E. A.: Effect of Hyaluronidase on Protective Urinary Colloids and Its Significance in Treatment of Renal Lithiasis, New Orleans M. & S. J. **104**:754-758, 1952.

354. Faber, V.: Streptococcal Hyaluronidase: Review and the Turbidimetric Method for Its Determination, Acta path. et microbiol. scandinav. **31**:345-354, 1952.

355. Di Caprio, J. M.; Rantz, L. A., and Randall, E.: Studies on the Streptococcal Hyaluronidase and Antihyaluronidase, A. M. A. Arch. Int. Med. **89**:374-386, 1952.

356. Wattenberg, O. W., and Glick, D.: Mucolytic Enzyme Systems: XVIII. Purification of the Non-Specific Hyaluronidase Inhibitor in Human Blood, Arch. Biochem. **35**:290-304, 1952.

357. Cole, J. W.; Cebul, F. A., and Holden, W. D.: Relationship of Liver to the Serum Nonspecific Hyaluronidase Inhibitor, Surgery **32**:828-834, 1952.

358. Rantz, L. A.; Di Caprio, J. M., and Randall, E.: Antistreptolysin O and Antihyaluronidase Titers in Health and in Various Diseases, Am. J. M. Sc. **224**:194-201, 1952

acid metabolism, have been synthesized and found to have marked antihyaluronidase activity.[359] Their possible role in medicine is being evaluated.

Streptokinase and Streptodornase

Streptokinase and streptodornase are separate enzymes that have been isolated from streptococci. They are usually marketed in combination as a commercial product, Varidase. Streptokinase stimulates the formation of a fibrinolytic enzyme, plasmin, from a normal plasma constituent, plasminogen. The reaction between streptokinase and plasminogen is apparently not one of catalysis. Rather, the reaction appears to be stoichiometric.[360] Its action, then, is to promote the lysis of fibrin clots. In experimental animals, it has been shown to lyse intravascular clots when injected intravenously.[361] Streptodornase, on the other hand, has a direct action against desoxyribonucleoprotein. It is thus useful in lysing the debris found in purulent wounds.

In ophthalmologic practice, streptokinase has been tried in the treatment of hyphema. However, end-results from its intraocular use are poor. Subconjunctival injection to promote the absorption of hemorrhage is also ill-advised because of the local tissue reaction.[362] As already mentioned, the use of an enzyme-antibiotic combination proved beneficial in the treatment of a corneal infection due to Ps. aeruginosa.[69]

The enzymes are widely used to lyse clotted blood and for the enzymatic débridement of infectious sites.[363] They assist, rather than replace, antibiotic therapy. These enzymes are not without their toxic effect, and pyrogenic and anaphylactoid reactions may occur.[364]

Trypsin

During the past few years, another proteolytic enzyme, trypsin, has become available and has gained extensive clinical use. This enzyme probably is lytic

359. Forrest, J.; Overell, B. G.; Petrow, V., and Stephenson, O.: Some Observations on the Inhibition of the Action of Hyaluronidase on Hyaluronic Acid by Gentisic Acid and Its Oxidation Products, J. Pharm. & Pharmacol. **4**:231-242, 1952. Hahn, L.: Inhibitors of Hyaluronidase, Nature London **170**:282-283, 1952.

360. Wasserman, A. E.: Streptokinase Activation of a Proteolytic Enzyme in Human Blood, Arch. Biochem. **41**:158-165, 1952.

361. Johnson, A. J., and Tillett, W. S.: Lysis in Rabbits of Intravascular Blood Clots by the Streptococcal Fibronolytic System (Streptokinase), J. Exper. Med. **95**:449-463, 1952.

362. Friedman, M. W.: Streptokinase in Ophthalmology, Am. J. Ophth. **35**:1184, 1952.

363. Knight, V.; Hardy, R. C., and Negrin, J. Jr.: Pseudomonas Aeruginosa Meningitis Treated with Streptokinase, Streptodornase, and Neomycin, J. A. M. A. **49**:1395-1397, 1952. Miller, J. M.; Long, P. H., and Stafford, E. S.: Clinical Experience with Streptokinase and Streptodornase in Tuberculosis, ibid. **148**:1485-1489, 1952. Miller, J. M., and Long, P. H.: Treatment of Hemothorax, with Particular Reference to the Use of Streptokinase and Streptodornase, U. S. Armed Forces M. J. **3**:1061-1070, 1952. Price, W. E., and Drinker, H. R., Jr.: Effect of Streptokinase-Streptodornase on the Urinary Bladder of the Dog and the Use of Streptokinase-Streptodornase for Dissolution of Clotted Blood in the Urinary Bladder of the Dog, Quart. Bull. Northwestern Univ. M. School **26**:377-380, 1952. Trice, P. A., and Townsend, T. E.: Meningitis Due to Klebsiella Pneumoniae: Use of Streptokinase and Streptodornase, J. A. M. A. **149**:1471-1473, 1952.

364. Baum, G. L., and Oransky, P.: Unusual Reaction to Intrapleural Administration of Streptokinase and Streptodornase, J. A. M. A. **149**:1012-1013, 1952.

against a greater variety of proteins than is the combination of streptokinase and streptodornase. It lyses fibrin readily[365] and has been shown to lyse intravascular clots.[366] An aerosol form is valuable in cleansing bronchiolar secretions.[367] Trypsin has been used in ointment form to clear necrotic debris and exudate from cutaneous ulcers.[368] The use of this enzyme has the same general clinical indications as does the streptokinase-streptodornase combination. There have been no reports of its use in the eye. However, the hazards attending the use of the streptokinase-streptodornase preparation should be considered to hold for trypsin as well, at least for the present. Unpublished experiences in my laboratory have indicated that the enzyme in solution has no untoward effect when instilled into the conjunctival sac of the rabbit provided the eye is uninjured. Also, subconjunctival injection appears to be well tolerated in animals. On the other hand, trypsin appears to have a marked deleterious effect on the cornea that has been abraded or denuded of its epithelium.

TOXICOLOGY

The reports of greatest interest in this field during the previous year have been those concerned with methyl alcohol poisoning. These included the report of an episode in the United States in which 41 deaths occurred among 323 persons who had ingested beverage contaminated with methyl alcohol.[369] Reports of fatal poisoning elsewhere from ingestion of this substance have also appeared.[370] Symptoms of this poisoning include visual disturbances, gastrointestinal disturbances, and headache. Death appears to be due to respiratory arrest in full inspiration. Convulsions may occur.

The visual disturbance consists generally of blurring of vision and is due typically to the development of a cecocentral scotoma.[371] Objective findings may include absence or impairment of the pupillary light reflex. Dilated, fixed pupils are said to carry a grave prognosis for life, and for vision if the patient survives. The early changes in the fundus include hyperemia of the disk, followed by peripapillary edema of the retina. When ocular damage is severe, atrophy of the disk is seen 30 to 60 days later.

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365. Astrup, T., and Sterndorff, I.: Fibrinolytic Activity of Tissue Extracts and of Trypsin, Nature, London **170**:981-983, 1952. Müllertz, S.: Fibrinolytic and Fibrinogenolytic Methods for Estimating Plasmin and Trypsin, Acta physiol. scandinav. **26**:174-182, 1952.

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367. Steigman, A. J., and Scott, C. H.: Trypsin in Poliomyelitis Patients with Tracheotomy, J. A. M. A. **150**:1403-1404, 1952.

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The reason for the metabolic disturbance and tissue poisoning which methyl alcohol causes is not certain. One of the enigmas lies in the fact that the quantity necessary to produce toxic, or even fatal, symptoms varies so greatly. Thus, in the episode mentioned above, only 15 cc. of methyl alcohol was fatal to one person, whereas one survivor had reportedly taken 500 cc.[369] A relatively constant feature of severe poisoning is pronounced acidosis. The cause of the acidosis is not known. Interesting experiments have been described which tend to indicate that the toxic effect of methyl alcohol on the retina is due to the inhibition of certain enzyme systems by formaldehyde.[372] This is an intermediate product in the oxidation of the methyl alcohol. Treatment is largely supportive. The acidosis should be combated by intravenous administration of sodium bicarbonate solution.

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Society Transactions

COLLEGE OF PHYSICIANS OF PHILADELPHIA, SECTION ON OPHTHALMOLOGY

George F. J. Kelly, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Dec. 18, 1952

Bullous Keratitis Associated with Dystrophy of Corneal Epithelium. Dr. Harold D. Barnshaw, Camden, N. J.

The patient, a male clerk aged 45, was first seen by me in March, 1949. He complained of feeling a bubble on the left eyelid, accompanied with slight pain. These symptoms had been present for approximately three weeks. During this period he had had refraction and new glasses had been ordered. His ocular and general medical histories were not significant.

Examination of the right eye revealed a small scar on the cornea close to the limbus at 6 o'clock. The scar was superficial and did not penetrate deep into the cornea. There were a few fine pigment deposits on the posterior portion of the cornea. The tension proved normal.

Examination of the left cornea revealed edema in the inferior temporal quadrant, with lowered sensitivity. The slit lamp showed the fluid to be in the epithelial layer. There were a few fine pigment deposits on the posterior portion of the cornea. The tension was low. The pupil was dilated with homatropine. At this time, a vitamin A preparation, 2% ethylmorphine hydrochloride, and hot compresses were ordered.

Two days later examination revealed a large single bulla, measuring 1.5 mm. in diameter, in the inferior temporal portion of the left cornea. The epithelial portion of the bulla was clear, as was the base. The bulla was removed with a cotton applicator and the base touched with iodine tincture.

The corneal changes advanced in spite of all treatment. He had local applications of iodine tincture U. S. P. and trichloroacetic acid. Atropine, ethylmorphine hydrochloride, zinc sulfate, phenacaine, sulfacetamide, and cortisone drops, and, an ointment containing cod liver oil were used. Hot compresses and pressure bandages were also employed. In addition, superficial keratectomy was tried.

In April, 1949, the patient was first seen in consultation by Dr. Alfred Cowan. Dr. Cowan's diagnosis was idiopathic bullous keratitis. His consultation reports are given in full:

"On April 23, 1949, the right eye was normal.

"In the left eye, gross inspection showed that the conjunctiva of the lids and of the globe was intensely injected. There was considerable ciliary injection. The lower half of the cornea was irregularly infiltrated, and the surface was unevenly elevated with a large white bleb below. The biomicroscope revealed that the epithelium over the entire cornea was edematous, in varying degrees. The epithelium over almost the entire lower quadrant was thickened, relucent, and elevated, forming a vesicle which contained clear fluid. The base of the vesicle, the anterior surface of Bowman's membrane, and the zone immediately behind showed intermittent increased relucence and irregular refractility. In the upper portions of the cornea there was a number of small vesicles, some with thickened epithelial surfaces. The epithelium was eroded in several places. However, for the most part, the edema of the epithelium over the upper part of the cornea produced only a bedewing. The stroma was irregularly relucent. There were no blood vessels in the cornea proper. Well-advanced endothelial dystrophy and numerous folds and ruptures in Descemet's membrane were present, but no other evidences of uveal involvement were seen.

"On June 29, 1949, the condition was essentially the same, but with a large area of denudation of epithelium in the center of the cornea. On Oct. 4, 1952, there were only slight ciliary and conjunctival congestion. The right eye was still practically normal. The epithelium over the entire surface of the left eye was edematous, the elevations varying in degree from moderate bedewing to dense bullae. The cornea was irregularly infiltrated throughout its entire thickness, with scattered, comparatively lucid areas. The portions of the posterior surface of the cornea which could be made out were characteristic of cornea guttata indicating entire disintegration of the endothelium. The anterior chamber was empty; the iris, as well as could be seen, was intact and active, and the lens was practically normal."

After Dr. Cowan's examination in October, he stated the opinion that the patient had epithelial and endothelial dystrophy of Fuchs.

At the time of this report, the patient's vision is 6/9 in the right eye and 6/30 in the left eye. The right eye shows little change except for some alterations in the endothelium. The left eye shows the pronounced epithelial changes, with superficial scarring, and many small bullae on the lower two-thirds of the cornea. The endothelial changes are prominent.

This case is more representative of the epithelial dystrophy of Fuchs than of any other condition. Fuchs first described this disease as an entity in 1910. He characterized it as follows: 1. The disease attacks elderly persons and is slowly progressive. 2. No inflammatory symptoms accompany the progress of the lesion. 3. There is a diffuse opacity of the cornea, most intense in the central region and shading off to a clear zone in the margin. 4. The corneal epithelium is roughened, is deficient in luster, and contains numerous vesicle-like elevations. Fuchs reported 13 cases of the disease, 4 in men and 9 in women. He noted that it was frequently associated with, but did not follow, glaucoma. Dr. William Zentmayer, in 1918, reported a case of bilateral epithelial dystrophy of the cornea in a woman aged 65. In 1926 H. and J. Friedenwald suggested that the endothelial changes were probably the primary phenomenon in typical cases of epithelial dystrophy.

The patient at present reported on is young for this disease, most patients being well over 50. In this case the edema, which usually starts in the central area, began in the periphery. However, there are definite degenerative changes in the epithelium, characterized by edema, bullous formation, and striae in the parenchyma. The endothelial changes have not played a prominent role in this case.

DISCUSSION

DR. ALFRED COWAN: Bullous keratitis is not a disease entity. It represents an advanced stage of corneal edema. It occurs in many ocular disorders—inflammatory, degenerative, and dystrophic.

In my opinion, this case is undoubtedly one of Fuchs's epithelial-endothelial dystrophy.

The condition which Fuchs chose to call epithelial dystrophy is not limited to the epithelium. Eventually it involves all the layers of the cornea—the epithelium, the entire stroma, Descemet's membrane, and the endothelium. It is even claimed by many that it does not start in the epithelium, but that the disease first attacks the endothelium. One might infer from much of the literature that always endothelial dystrophy is actually the first stage of involvement of the rest of the cornea.

I do not agree with those who maintain that endothelial dystrophy, even the most advanced form, is necessarily the early manifestation of eventual dystrophy of the entire cornea. Fuchs's epithelial dystrophy is rare; endothelial dystrophy is common. I have had under observation for years patients with endothelial dystrophy that has progressed to disintegration of the entire endothelium—guttate cornea—without the slightest indication of involvement of the anterior layers, and with comparatively little loss of usefulness of the eyes.

Neither, in my experience, does the endothelium act as a barrier to prevent fluid from the anterior chamber from entering the cornea, and subsequent edema. The theory that the diseased endothelium allows fluid to pass through it does not seem to hold. For years I have seen eyes with total absence of endothelium with not the slightest evidence of edema. Other factors must be present. Cogan's theory, i. e., that the edema and the epithelial changes are due to an osmotic imbibition of fluid from the tears, is much more tenable.

Treatment of Opacities of the Cornea by Desiccation. Dr. William M. Hart and Dr. Louis F. Hinman.

In 1946 preliminary observations were presented before this group on the physical and chemical factors affecting the transmission of light by the cornea and sclera. This was followed later by publication in the Archives (Arch. Ophth. **40**:601-612; 612-623 [Dec.] 1948). The observation was made at that time that corneal opacities could be made to disappear in vitro in one of two ways: (1) simply by drying the cornea in air, or (2) by hydration in suitable solutions. The physical reasons for this were given. In the present paper, data were presented on the treatment of interstitial opacities in dogs due to distemper. A thorough desiccation of the cornea with dry air was followed by gradual disappearance of the opacity over a period of three to six weeks. Only a fine interstitial haze remained as a permanent sequela. The results in three human cases were also presented: one case of interstitial syphilitic opactiy and two cases of opacity following unsuccessful keratoplasty. The eyes were in very poor condition before treatment began, and so the objective benefits obtained were of little practical importance in improving vision. The desiccation technique, to be described elsewhere, was not offered as a method of therapy at this time; at present it serves only to demonstrate the physiological potentialities of the opaque cornea.

DISCUSSION

Dr. Glen G. Gibson: This interesting investigation on the effects of partial desiccation of the normal and the diseased cornea brings up many points for discussion. I shall mention only a few.

It has been my privilege from time to time to observe both the patients and the dogs upon whom this procedure was performed, and I should like to congratulate the authors not only on their effort, but also on the conservative and accurate nature of their work and their presentation.

Their material was selected with two dominant considerations in mind. First, in an effort to avoid the error of attributing improvement to their work which was due to the natural improvement of opacities in the cornea, they selected patients whose disease was long-standing, well past the possible edematous phase of lesions, the permanent nature of whose corneal opacities could not be doubted. Second, only patients whose corneal opacities were of maximum extent and maximum depth were selected, so that only those patients who had, so to speak, nothing to lose by this procedure were represented. The authors accepted these obvious disadvantages because of the possible potential dangers which might be inherent in a procedure involving such a profound desiccation.

Dr. Hart failed to point out the intense nature of this drying. The cornea was really desiccated in a very thorough manner. The authors were concerned about such dangers, for example, as the decrease in corneal immunity, with resulting infection, and interference with the functional integrity of the corneal endothelium, either of which might add to, rather than subtract from, the amount of corneal opacity. Furthermore, the material which they selected did not represent any specific clinical entity but, rather, constituted a heterogeneous group of conditions. Therefore, the term "corneal opacity" is used in the widest sense.

One was formerly content to regard corneal opacities merely from the microscopic point of view, and one considered the loss of transparency to be adequately

explained by cellular and fibroblastic proliferation and the distorted arrangement of the corneal lamellae secondary to the pathology. It is becoming increasingly evident that a more intimate concept of the chemical composition of opacities must be formulated. The remarkable clearing that occurred in these corneas suggests that it may be necessary to modify one's former concept beyond the microscopic level. The work suggests that even in nonedematous corneal opacities water contributes in a large measure, both mechanically and chemically, to the derangement of the optical properties of the cornea. These facts have never been suspected on the basis of microscopic observations.

An honest and accurate evaluation of this work is not only difficult but perhaps premature. What has been accomplished is an adequate demonstration that corneal opacities can temporarily be cleared with surprising ease and speed. The authors have demonstrated that this can be done, and that it can be repeated without apparent damaging effect to the eye. What remains to be done, beyond this first stage of their work, is the demonstration that the clearing they have attained can be maintained in sufficient amount and in a sufficiently lasting form to be of real clinical value. It is to be hoped that in the future this method, or a modification of the technique perhaps to include drying of the posterior, as well as the anterior, surface, may be used to control other factors in the basic corneal processes. It must be clearly understood, however, this work has not progressed beyond the experimental stage. It is by no means sufficiently effective to be recommended as an acceptable method of treatment of corneal opacities.

Dr. Francis Heed Adler: I should like to emphasize, as Dr. Gibson has, that experiments of this sort are brave attempts to explore a field that has so far been particularly barren on the side both of clinical medicine and of research. We are now, fortunately, in a position where we feel rather well founded in the belief that Cogan and Kinsey's theories of corneal turgesence and transparency are correct. They have not been entirely substantiated, and I am sure Cogan and Kinsey themselves would be the first to admit this. So far, their theory is the best one that has been presented, but we must not fail to explore further possibilities.

These experiments go no further in showing clearing of opacities of the cornea than those well-recognized agents, such as glycerin, which clear the corneas turgescent with edema temporarily. One is not wiser from these experiments as to what is the fundamental cause of the opacification in these cases, but they represent an earnest and honest attempt to find the truth, and therefore the authors should be congratulated.

Dr. Louis F. Hinman: I should like to call to the attention of ophthalmologists how fortunate we are that the Lord, and tissue tolerance, keep us out of so many difficulties. These corneas were dehydrated almost to an amorphous mass, and to see them again returned to the semblance of normal was a revelation. The work suggests that perhaps there is a place for use of stored corneas, rather than for immediate transplantation of corneas, in treatment of corneal opacities.

At the risk of being a bit of a heretic, I should like to mention my observation concerning vascularization. In several of these cases, prior to improvement in the appearance of opacities, neovascularization was observed, and it may very well be that vascularization is not quite the ominous process we have considered it. It may in some way contribute to clearing of the cornea after injury.

Dr. William M. Hart: We did not emphasize that the beneficial effect of this treatment on corneal opacity is biphasic. Acutely, the opacity disappears with desiccation; this result superficially, makes it appear that simple withdrawal of water is all that is concerned. The opacity reappears on rehydration. However, there follows a period during which the clearing effects reappear and become permanent. This result was a surprise to me. I was so intrigued with the mechanical concept that I had visions of the cornea clearing immediately and staying that way. The experience serves only to emphasize that the physiochemical factors have been no more than enumerated. We do not know their quantitative relations

to each other. However, regardless of mechanisms, the encouraging thing from the practical standpoint is that fibroblastic invasion and scarring need not be regarded as hopeless.

Long-Lasting Local Anesthetic Agents in Ophthalmic Surgery. Dr. Harold G. Scheie and Dr. Richard G. Ellis.

Observations were presented on the experimental and clinical use of Efocaine and a substance designated as U-0045, two local anesthetic agents having a considerably longer action than procaine. There are obvious advantages in local anesthesia of sufficient duration that postoperative pain in intraocular surgery might be avoided. Efocaine, a local anesthetic which embodies a new approach to prolonged anesthesia, has recently been introduced for clinical use. It is made by dissolving water-insoluble procaine base in polyethylene and propylene glycol. When this solution is injected into the body, upon contact with tissue fluids the procaine crystallizes out of solution to form an anesthetic depot, which requires a week or more to absorb. The anesthetic remains effective during this time. Still more recently, a local anesthetic agent designated as U-0045, was made available to us by our department of anesthesiology. U-0045, or bis-[β-(*o*-methoxyphenyl)-isopropyl]-amine, differs chemically from the procaine group of anesthetics in that it is a secondary amine and contains no ester linkage, as does the procaine group. Because of this structure, it is less susceptible to hydrolysis by tissues and therefore has a more prolonged anesthetic action than has procaine. Like procaine base, it is insoluble in water; but the salt, U-0045 lactate, which was used in our work, is soluble up to 5%. Bass and Schroeder found it to be four times as toxic as procaine, but it is 40 times as effective an anesthetic agent. This ratio gives it a therapeutic advantage of nearly 12 times, so that it can be used with safety.

We compared the effects of retrobulbar injections of procaine, U-0045, and Efocaine in rabbits. Procaine was found to be effective for an average of 60 minutes, but when combined with hyaluronidase its effect lasted only 33 minutes. The shortened duration of action when combined with hyaluronidase was probably due to the more rapid diffusion through the tissues, with prompter elimination of the local anesthetic. U-0045 lactate maintained an effective block of the ciliary nerves for an average of 312 minutes, but when combined with procaine this period of effectiveness was reduced to 258 minutes. The anesthetic effect of Efocaine was still more persistent, lasting 11 days or longer in nearly all instances.

In rabbits, U-0045 caused very little local reaction as compared with Efocaine, which was extremely irritating. Retrobulbar injections of Efocaine caused rather severe proptosis and conjunctival edema. Injection of the anterior chamber caused permanent corneal opacity with corneal vascularization. Intracorneal and subconjunctival injections were likewise extremely irritating, as compared with U-0045.

Clinically, Efocaine produced effective retrobulbar anesthesia, varying from one week to two months. However, the drug caused so much reaction in the six patients in whose eyes it was employed that we discourage its clinical use. Exophthalmos and edema of the lids always occurred. One patient had weakness of the superior rectus muscle with ptosis, which lasted two months.

Our clinical experience with U-0045 was more encouraging. When instilled into the conjunctival cul-de-sac, a 0.2% solution produced corneal anesthesia for a longer time than did 1% tetracaine hydrochloride. It caused more local irritation in patients but produced no damage to the corneal epithelium.

It was used for retrobulbar injection in over 100 patients for various types of intraocular surgery. U-0045 lactate alone produced excellent anesthesia, lasting from 7 to 12 hours. Akinesia of the extraocular muscles was not as satisfactory as the akinesia that we had been obtaining with procaine. We therefore combined U-0045 lactate with procaine in the same solution and used this combination in 95 patients. The anesthesia was universally good and the akinesia of the extraocular muscles excellent. The anesthesia, as a rule, lasted eight hours; consequently,

postoperative pain was greatly diminished. Only an occasional patient complained severely enough to need an analgesic, and postoperative vomiting was almost eliminated. We believe that this anesthetic agent represents a real advancement in the postoperative management of patients who have had ocular surgery.

DISCUSSION

DR. JAMES E. ECKENHOFF: For years there has been an attempt to increase the comfort and safety of the patient during operation and in the postoperative period by the preoperative employment of drugs. All are familiar with the once popular use of basal narcotics to increase the patient's comfort before, during, and after operation and to decrease the incidence of complications. As you know, this method decreased, rather than increased, the safety of the patient; so it has generally been abandoned. Along the same lines, local anesthetics have been injected during or immediately after ophthalmic surgery for the purpose of relieving pain. Here, again, they have not been uniformly successful, and for the most part have been abandoned.

Two years ago a detail man tried to sell us Efocaine on the basis that it was a drug that could be given for nerve blocks the night before operation, and the next morning the patient would have good anesthesia for his operation and little pain for 8 to 10 days afterward. It sounded attractive, but somehow impractical. However, we did try the drug for a large number of nerve blocks and have obtained a considerable experience with it. Blocks have been satisfactory in about 75% of the patients, but the complaints of the rest have made us abandon the drug. The complaints have been of pain upon injection; pain in areas adjacent to that region blocked—for example, pleuritic pain following stellate-ganglion block—and pain in blocked areas after disappearance of the anesthesia.

About eight months ago Dr. Scheie asked our opinion of the use of Efocaine for ophthalmic surgery. With our experience, we were not particularly enthusiastic and advised caution. The results Dr. Scheie has reported show that our opinion was probably correct.

About the same time we were working with methoxyphenamine (Orthoxin) hydrochloride and suggested that Dr. Scheie might like to employ this drug. We had performed about 100 regional blocks with it and found it to be an effective anesthetic. Onset of the blocks seemed to be slower than with procaine, but the duration of anesthesia was considerably longer, as long as four or five hours. It is of interest, in view of the difference Dr. Scheie found between the duration of objective signs of block, of 47 minutes, and that of subjective signs, of 77 minutes, that many of our patients had subjective relief of pain for hours after the block had apparently worn off.

We have found one toxic effect of the U-0045, and that has been hypotension. However, we employ considerably larger quantities of the drug (25 to 40 cc.) than are used in ophthalmic surgery. I should like to ask Dr. Scheie whether he noticed any toxic symptoms with this drug?

It worries me that we have employed this drug intrathecally in 85 patients. The anesthesia has been uniformly satisfactory, and we have seen no postanesthesia neurologic sequelae. I believe, however, in view of the tissue reaction that Dr. Scheie observed after instillation of the drug into the conjunctiva, that we should abandon the use of the drug for spinal anesthesia, pending further study. We proceeded to use the intrathecal injections after satisfactory results in a large series of animals.

Finally, I should like to ask Dr. Scheie whether he has attempted to explain why Efocaine is a tissue irritant? After all, it is procaine; yet it does irritate tissue.

DR. FRANCIS HEED ADLER: When Dr. Scheie first talked to me about U-0045 and its possibilities, I said, "Well, my patients don't have any pain after procaine injection." Then he asked me, "Well, do you come around and see them three or four hours after operation? I said, "No." The way to evaluate a patient's

postoperative pain is to ask the resident about it. The patient is much more comfortable, according to our residents, when we use U-0045 than when we were using procaine. I feel certain that the anesthesia lasts longer and that the patients are more comfortable. When I come around and ask them whether they have any pain, they all say "No"; but then that is next day.

I do think it takes somewhat longer for the anesthetic to act. Is it not true that you have to wait longer for U-0045 than for procaine to take full effect?

DR. SOLOMON S. BRAV: Has Dr. Scheie employed this drug for akinesia, i. e., as an O'Brien block, or has he used it only as a retrobulbar block?

DR. GEORGE F. J. KELLY: Have either one of these drugs been used in cases in which there was already pain? In most of the cases that have been talked about the pain was postoperative in type. Have they been used by the neurosurgeons for relief of pain, such as occurs in tic douloureux?

DR. JAMES E. ECKENHOFF: There has been a good deal of work with the drug for the relief of pain. Fifty to 60% of my own experience has been in the treatment of chronic pain of various causes. The drug (U-0045) has been employed for relief of intercostal neuralgias, for sympathetic blocks in the relief of autonomic dystrophies, and, I believe, for tic. It has been employed by others to relieve pruritus ani, with the injection of occasional enormous doses. One author reported the use of 15 cc., and he was surprised by the development of rather a wide slough. The results have been much as have already been described.

DR. HAROLD G. SCHEIE: I should like to point out the significantly longer duration of anesthesia in patients than in our animals. This probably resulted from the use of 1 cc. of a 0.5% solution in patients as compared with the injection of 0.5 cc. of a 0.2% solution in animals. We occasionally found that anesthesia lasted over 12 hours in patients, a period sufficiently long that nearly all postoperative pain was avoided.

In answer to Dr. Eckenhoff's question, we have observed no toxic symptoms from the amount of U-0045 which we have used. I should think one would use this substance intrathecally only with hesitation in view of the irritation from conjunctival instillation, and, probably more important, because injection into the anterior chamber caused corneal haze in 5 of 11 eyes.

Dr. Adler has mentioned the incidence of postoperative pain after intraocular surgery. We find that it is present for four to six hours in most instances. Our nurses are very grateful for U-0045, because through avoidance of this period of pain their work is made much easier and their problem of postoperative care is much simpler.

Dr. Brav asked whether we used it for facial akinesia. We have not, because the duration of akinesia from procaine is always sufficiently long.

George F. J. Kelly, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

Feb. 19, 1953

Galactose Cataracts. DR. EDWARD CANNON and DR. JOSEPH RITTER (by invitation).

The case of a 4½-year-old girl with galactose cataracts was reported. Her main signs and symptoms, in addition to zonular cataracts, were hepatomegaly, retarded physical development, increased total blood sugar, and melituria. The specific sugar in the urine was identified by paper chromatography. Discission was performed on one cataract; the other did not show regression after the child had been on a milk-free diet for eight months; other signs did regress.

Galactosemia is considered an inborn error in the metabolism of ingested galactose. Galactose diffuses readily through body tissues, and the physiopathologic

aberrations of various body structures and functions which are noted in this entity is probably on a toxic basis. There is a considerable body of experimental data in the literature concerning in vivo and in vitro effects of galactose on the rat lens.

DISCUSSION

DR. HARRY GREEN: Our knowledge of the metabolic behavior of galactose may be summarized by the following equations:

$$\text{Galactose} + \text{ATP}^* \longleftrightarrow \text{Galactose-1-PO}_4 + \text{ADP} \quad (1)$$

$$\text{Galactose-1-PO}_4 + \text{UDPG} \longleftrightarrow \text{Glucose-1-PO}_4 + \text{UDPGa} \quad (2)$$

$$\text{UDPGa} \rightleftharpoons \text{UDPG} \quad (2a)$$

$$\text{Glucose-1-PO}_4 + \text{Glucose-1,6-DiPO}_4 \longleftrightarrow \text{Glucose-6-PO}_4 + \text{Glucose-1,6-DiPO}_4 \quad (3)$$

Where ATP indicates adenosinetriphosphate; ADP, adenosinediphosphate; UDPG, uridinediphosphate glucose, and UDPGa, uridinediphospate galactose.

The enzymes involved in the above reactions are, respectively, hexokinase, phosphogalactoisomerase, and phosphoglucomutase, while adenosinetriphosphate, uridinediphosphate glucose, and glucose-1,6-diphosphate are the corresponding coenzymes. The product glucose-6-phosphate is subsequently metabolized, in accordance with the classic glycolytic scheme of Embden and Meyerhof, to pyruvic and lactic acid. Whether similar reactions occur in the lens is not known.

In the normal lens the major source of energy is glucose, although the metabolic pathway that glucose travels to lactic acid in the lens is still not entirely known. Müller, in 1937, found that, with bovine eyes, as the age of the lens increased the rate of glucose disappearance was diminished. With the inception of cataract formation, this rate was further decreased until in a mature cataract hardly any carbohydrate metabolism was measurable. It is reasonable to assume, therefore, in our present state of knowledge of lens metabolism, that a slowing down of the normal rate of glucose ultilization by the lens, for whatever reason, may predispose to the development of cataract.

The above-described reactions were examined for the purpose of speculating as to the ways in which excess galactose or the accumulation of galactose-1-phosphate could disrupt the sequence of events. It was tentatively suggested that in the normal lens small amounts of galactose are readily metabolized, presumably in accordance with the above reactions. In galactosemia, however, the normal carbohydrate metabolism may be interfered with at any of the indicated stages, thereby causing a derangement in the mechanism for the generation of energy necessary for protein synthesis, fat metabolism, growth, maintenance of transparency, etc.

Simulated Progression of Visual Field Defects in Glaucoma. DR. ROBERT M. DAY (by invitation).

An experimental and clinical study of three factors which may cause simulated progression of the visual field defects in glaucoma was presented. These three factors are (1) loss of transparency of the ocular media (cataract formation, particularly of the diffuse nuclear type); (2) artificial myopia associated with ciliary spasm, which results from the use of miotics in nonpresbyopic eyes; (3) miosis. All these factors cause a reduction in the intensity of the retinal stimulus by the test object.

The following conclusions were reached:

1. Visual fields of nonpresbyopic patients with glaucoma should not be taken until after any accommodative spasm induced by miotic therapy has subsided.

2. When the visual fields in glaucomatous patients are charted, the pupils should ideally be of the same size during subsequent examinations.

3. Increasing myopia associated with decrease in the size of the visual field in glaucomatous eyes suggests the progression of lens changes.

4. Increasing lens changes often explain the progression of visual field defects following the control of glaucoma by either miotics or surgical means.

5. In following the course of glaucoma by means of the visual field studies, the status of the optical media should be carefully evaluated, for opacities, i. e., cataract formation, may cause an apparent loss of field and so lead to unwarranted surgery.

DISCUSSION

Dr. Harold G. Scheie: The greatest benefit thus far derived from the arguments of advocates of the neurovascular and the gonioscopic schools of thought regarding glaucoma has been in the management of the disease. Both schools emphasize the importance of distinguishing between acute and chronic glaucoma, and there is increasing agreement that different therapeutic approaches should be employed for the two types. Surgical intervention is advised in acute congestive glaucoma, while chronic simple glaucoma should be treated medically as long as damage to the eye can be prevented by this means. The prime indications for surgery are uncontrolled tension or increasing visual field defects. Since the ocular tension and visual fields are of such great importance, misleading results from visual field studies are as unpardonable as inaccurate tonometry.

We should be thoroughly familiar with any factor which might simulate progressive loss of visual fields and serve as a false indication for surgical intervention. Dr. Day has mentioned refractive errors, miosis, and cataractous changes, all of which may cause apparent increase of visual field defects by reducing the intensity of the retinal stimulation from a test object of given size. He has mentioned the precautions which should be taken, such as recording the visual acuity in younger persons, in whom artificial myopia might be induced by miotics. He also mentioned the wisdom of recording the size of the pupil and urged taking visual fields at the same interval after instillation of the miotic.

Care should be taken to recognize nuclear cataractous changes. This may be difficult through small pupils, but if the angles are open, the pupil can be safely dilated for examination of the lens and evaluation of the nerve head. I have never seen increasing loss of visual field in the absence of progressive excavation of the optic nerve. Nuclear lens changes are usually accompanied with increasing myopia. One's judgment should balance these against other clinical signs, such as the level of tension and the age of the patient. Emphasis is to be placed on the avoidance of surgery in this type of glaucoma whenever possible. Increasing lens changes very frequently cause apparent loss of visual fields following normalization of tension by filtration procedures. I have seen several patients in one glaucoma clinic whose eyes seemed to have continued to deteriorate after normalization of tension by corneoscleral trephination. However, they all showed increasing myopia due to cataractous changes, as shown by Dr. Day; and after cataract extraction the visual fields returned to their original state. This serves as an argument against progressive loss of visual fields of a glaucomatous nature from purely vascular degeneration.

Dr. George F. J. Kelly: As Dr. Day stated, after glaucoma surgery it has been thought that the visual field became smaller, even though the tension was reduced and stayed reduced, whereas actually the visual field had remained the same but was not properly determined.

The findings in the eye with cataractous changes, which in 1939 showed an arcuate scotoma and then in 1949, after operation, showed no arcuate defect, are most unusual. My only explanation for this is that the arcuate defect, in 1939, was relative. If that defect had been absolute, and most arcuate defects are absolute, it should not have recovered.

With regard to the contraction of the internal isopters, causing baring of the blind spot, after the use of pilocarpine, I wonder whether miosis explains the whole story. One must also consider that pilocarpine has some action on the vasomotor system.

I have seen in many cases of mild glaucoma in which the visual fields showed a baring of the blind spot, that after the use of pilocarpine the internal isopters would be larger and no baring would be evident.

DR. ROBERT M. DAY: In answer to Dr. Kelly, I interpreted the disappearance of the arcuate scotoma when the cataract was removed by the fact that test objects of the same size were used. A cataract in effect decreases the stimulation of the retina. In other words, it has the same effect as the use of a smaller test object. The arcuate scotoma was not charted, but it would be my interpretation that it is still there and that it could be found with a smaller test object. As to the improvement of the field which occasionally follows the control of tension, I am sure that another factor is present there. This factor was not considered at all in this discussion.

Cataracts in Alloxan Diabetic Rabbits. DR. DAVID NAIDOFF, DR. IRWIN J. PINCUS, DR. ARNO E. TOWN, and MR. M. E. SCOTT (by invitation).

Alloxan was injected in varying doses and at varying rates intravenously into 107 rabbits. Of the 67 animals which survived after five days, 32 had definite diabetes.

Lenticular changes were observed in every diabetic animal, and these changes were seen in both eyes, in which they were of equal severity. It is believed that these changes occur in the first 24 to 48 hours after the injection of the alloxan in these diabetic animals, and that they first appear as an increased density or as faint striations in the equator.

The changes progress in a definite pattern, and at the end of the first week they can be seen as tiny vacuoles in the equatorial zone in the cortex. The vacuoles, in turn, appear to coalesce; more opacities form, and, eventually, by the 16th week the lens is so cloudy in severely diabetic animals that the fundus cannot be seen. Slit-lamp examination shows the changes to be most pronounced in the posterior cortex and about the equator.

Frequent examinations of the rabbits showed that the lens changes varied remarkably from day to day. Although the pattern of the cataract development was constantly changing, a definite progression did occur, and its extent and severity apparently depended upon the severity and the duration of the diabetes.

These diabetic animals showed lens changes the degree of which fluctuated very greatly, and concomitant observations of the blood sugar levels and urinary glucose outputs revealed striking fluctuations at the same time. These lens changes were of such a degree as to give the impression that up to a certain point they were reversible.

DISCUSSION

DR. I. H. LEOPOLD: Diabetes mellitus is not a disease entity but a syndrome characterized by hyperglycemia and glycosuria. So defined, diabetes mellitus can be produced by several experimental methods. This picture can be produced by removing the pancreas in experimental animals. Recently, by removal of the pancreas of a patient who has had a malignant neoplasm of the pancreas, the clinical symptoms of diabetes mellitus have resulted. The findings closely resemble those found in experimental pancreatectomy and in clinical diabetes, but the insulin requirements rarely exceed 25 to 40 units a day for a patient maintained on a diet of 250 gm. of carbohydrate, 100 gm. of protein, and 100 gm. of fat. This may signify the existence of a hyperglycemic factor in the pancreas which is necessary to bring about the high blood sugar levels that occur in clinical diabetes mellitus. Such a factor has been isolated from impure insulin and from the islets.

By injecting anterior pituitary extracts daily and increasing the dose every few days, one can produce in a dog a diabetic state which persists indefinitely even

though the injections are discontinued. The treatment must be continued for a few weeks, however, before this state is obtained. The only discoverable change histologically is in the islets. They show varying degrees of involvement, ranging from depletion of the beta cells to complete disappearance of the islets and their replacement by hyaline tissue. These animals differ from depancreatized dogs in several respects. They can survive for long periods without insulin.

Repeated and prolonged injections with thyroid hormone damage the islets similarly. The histologic injury obtained, however, is less severe than that induced by anterior pituitary extracts or by alloxan. A permanent diabetic state can be produced in this manner only if a portion of the pancreas has first been removed.

It has been claimed that ingestion of excessively large amounts of carbohydrates over a long period will first stimulate, and finally exhaust, the islet cells, leading to their permanent destruction. This is an extremely difficult method with which to produce experimental diabetes mellitus.

Another method is by the use of alloxan, and this is the one employed by Dr. Naidoff and his co-workers in their experiments. Alloxan is a specific poison for the beta cells of the islets.

It is important to realize that in a human with diabetes mellitus gross microscopic changes in the pancreas are rare. Edema of the beta cells has been demonstrated. However, usually no anatomical site for the clinical diabetes mellitus can be found. This fact must be kept in mind in evaluating any ocular changes produced by experimental diabetes mellitus.

Of the several experimental methods for the production of diabetes mellitus, a few have been employed for the production of experimental cataract. Dr. Naidoff and his group have used the method of alloxan injection. Foglia and Cramer employed pancreatectomy in 1944 and were able to produce cataracts in all rats from which 95% of the pancreas had been removed. These cataracts developed within 50 days. When 80% of the pancreas had been removed, the cataracts developed more slowly, taking approximately 200 days.

There are several possible mechanisms by which cataracts may be formed in diabetes mellitus. It may be that they result from hyperglycemia. The observations of Dr. Naidoff and his co-workers tend to support this mechanism. Patterson, in 1944, produced cataracts experimentally by the intravenous injection of dehydroascorbic acid and related compounds in rats. A hyperglycemia is produced with these agents through a mechanism of partial saturation of the renal-tubule reabsorption pathway for glucose. Patterson was able to correlate the onset of the cataracts with the severity of the hyperglycemia. When the blood sugar was high, the cataracts developed in 8 to 10 weeks; when the blood sugar was lower, the cataracts were slower to develop and were often unilateral. Another possible mechanism is interference with enzyme metabolism within the lens. Bellows found that the glutathione concentration of the lens was reduced within 72 hours after the administration of alloxan. Dr. Naidoff and his co-workers have demonstrated that the earliest changes in the lens could be detected within 24 hours after the administration of alloxan. Thus, since depletion of glutathione does not occur for three days, it would appear that this is not the fundamental factor, as the cataractous changes precede the glutathione depletion. Other mechanisms for the production of the cataracts must be considered. Edema and degeneration of the ciliary epithelium as the result of hyperglycemia perhaps might lead to changes in the lens on a nutritive basis. Alterations in the permeability of the capsule, hydration of the lens by alterations in the osmotic pressure relationship, and hormonal imbalance are all possible means by which the lens vacuoles, fissures, and opacities develop.

Bellows and Shoch, in 1950, noted that the earliest changes in the lens took place at the periphery and consisted of small vacuoles. Dr. Naidoff and his coworkers confirmed this site of initial change. However, the authors' experimental reports showed the onset to be within 24 hours.

I was impressed with the fact that Dr. Naidoff, Dr. Pincus, and Dr. Town could employ a method that has been available for many years, and has been used repeatedly by many workers for the production of cataract, and could by painstaking and thorough research add something to our knowledge of the formation of experimental diabetic cataracts.

I look forward with great interest and anticipation to the continuation of these studies.

DR. I. S. TASSMAN: The results of experiments on animals of this kind are not always significant of just what occurs clinically. There are one or two questions with regard to the conclusions and the conduct of the experiment. I wonder whether ophthalmoscopic examination of the fundus was made in those eyes in which it was possible to do so, and whether the presence of any retinopathy could be recognized. There are certain factors no doubt present in the diabetic state in humans which do not enter into a problem of this condition in rabbits. Becker and Friedenwald, at present at the Wilmer Ophthalmological Institute, are conducting studies with regard to the occurrence of retinopathy in alloxan-diabetic rabbits and the effect of administration of corticotropin in diabetic rabbits. They have up until the present time, I believe, found that retinopathy occurs in the diabetic rabbits that have also received corticotropin. The alloxan-diabetic rabbits that have not received the corticotropin showed no retinopathy, and in the control group, or nondiabetic rabbits, the retinopathy was absent.

If a complete cataract develops in these eyes in the short period of time that was mentioned, it would prevent an ophthalmoscopic examination of the fundus, but in the eyes in which it was possible to examine the fundus, I wonder whether any evidence of retinopathy was present. As Dr. Leopold stated, there are decrease and loss of glutathione in the lens with the development of cataract, and in the mature cataract, even in the human eye, it has been found that glutathione is absent, or almost entirely so. However, I do not think Bellows should be given the credit for this. This was demonstrated long before, by Adams, in England, and at about the same time by someone in this country, whose name escapes me at the moment.

DR. JOSEPH WALDMAN: I wanted merely to ask about the protecting action of dimercaprol against alloxan, and Dr. Pincus tells me that he did not go into that phase of it.

DR. I. H. LEOPOLD: Dr. Bellows was not the first to describe the loss of glutathione from the lens in which a cataract develops as a result of a toxic agent. However, he did observe the loss of glutathione associated with the development of cataracts after the administration of alloxan, and it is this fact that I mentioned. Dr. Waldman asked concerning the possibility of dimercaprol being used to prevent or clear up the opacities of the lens induced by alloxan diabetes. Lazarow demonstrated in 1944 that the use of glutathione could prevent the damage to the islet cells by alloxan. Buschke attempted to prevent the development of cataracts following the use of naphthalene and galactose with dimercaprol. Both these toxic agents, naphthalene and galactose, cause a disappearance of glutathione from the lens. Buschke was unable to influence cataracts which had already started by employing dimercaprol. Cysteine is a constituent of glutathione which contains the all-important sulfhydryl radical. Others have shown that if cysteine was employed prior to the development of galactose or naphthalene cataract, the lens damage would be somewhat reduced.

DR. I. J. PINCUS: I agree heartily with Dr. Leopold that the study of the eye in relation to metabolic disturbances is an extremely fascinating field. We have studied a number of factors in our animals and attempted to correlate these with the changes in the eye. Lipid analyses of the blood and liver have been made, and, although these levels were related to the blood sugar level in a general way, there were striking exceptions, and it was apparent that only an indirect relationship existed between the lens changes and the blood or liver lipids. Our animals were well

studied in regard to their "diabetic" state. I think it of interest that some of our animals have lived as long as a year after the administration of alloxan with blood sugar levels as high as 600 mg. per 100 cc.; these animals appeared well nourished, frequently gained in weight, and seemed quite well. Despite the fact that insulin was not administered to any of these animals except for one small group, not one showed chemical or clinical evidence of acidosis. The alloxan-diabetic animal does not resemble the usual diabetic patient, and this is particularly true of the rabbit. The only factors with which the ocular changes were directly related were the blood sugar levels, urinary glucose excretions, and the duration of the "diabetes."

Since the report from the Hopkins group, we, too, have been interested in the retinal changes following corticotropin which they reported. A group of rabbits severely diabetic after the injection of alloxan were given varying doses of cortisone. These animals promptly became very ill, they lost weight, and several died; the remainder were killed, and a thorough study of the kidneys, heart, retina, and other tissues showed no evidence of a vascular disturbance. Whether corticotropin will have other effects we do not know.

Our studies on the lens are continuing, and we hope to have more to report in the near future.

DR. DAVID NAIDOFF: Although most investigators of this problem have stressed the similarity of alloxan diabetes to human diabetes, we have not made any attempt to correlate the two conditions in this study. I should have mentioned that the fundi of all the animals were examined routinely, but we were never able to demonstrate any diabetic retinopathy. We also tried to produce diabetic retinopathy in alloxan-diabetic animals by giving them injections of cortisone. The diabetes in our rabbits immediately became severer, and the animals died very soon thereafter. Again, no retinopathy was observed, but it should be stated that in these rabbits lens changes were severe enough to prevent a thorough examination of the fundus and that the rabbits used had been severely diabetic for a long time prior to the injection of cortisone.

George F. J. Kelly M.D., *Chairman*

M. Luther Kauffman, *Clerk*

March 19, 1953

Bilateral Metastatic Carcinoma of Uveal Tract with Orbital Extension. DR. CARROLL R. MULLEN, DR. PERCE DELONG, and (by invitation) DR. CHARLES G. STEINMETZ JR.

Metastatic carcinoma of the uveal tract was first reported in 1872. A review in 1936 revealed 229 cases, of which 156 were histologically verified; in 20.8% the involvement was binocular. The occurrence in clinical patients varies from 1:30,000 to 1:150,000. It is the most frequently encountered secondary tumor of the eye and is believed to be more frequent than the literature indicates.

The primary site of the neoplasm in women is the breast, and in men, the lungs. This incidence is not consistent with the incidence of the primary tumor throughout the body but is influenced by the viability and the ability of the cells to implant after the cells have metastasized. Anatomical directness of the arteries is responsible for more frequent involvement of the left eye than of the right. The most usual site of choroidal metastasis is the temporal side of the posterior pole near the macula.

Histologically, the tumor depends upon the nature of the primary growth and may be medullary, scirrhous, or adenomatous. The tumor cells spread from their metastatic site in the lines of least resistance, along the lymph spaces and between the planes of the choroidal stroma.

Treatment in these cases is palliative. Irradiation of the globe inhibits the spread and maintains useful vision to the end.

Miss B., a white woman aged 56, was seen in the office of Dr. Carroll R. Mullen with the chief complaint of bilateral diminution of vision, starting three months after a right radical mastectomy. Extensive involvement of the axilla was noted at operation. Studies with radioactive phosphorus gave positive results in both eyes, with 120% variation from mean in the right eye and 110% in the left eye.

X-ray examination of the chest showed rapidly extending metastatic involvement. Necropsy disclosed extensive metastatic lesions in all organs. The globes were sectioned along with the orbital contents. The left eye showed a flat choroidal tumor involving the entire posterior segment. The retina was completely detached. In the right eye the picture was similar, with extensive involvement and detachment. However, the anterior segment was involved, especially the ciliary body, with tumor cells breaking into the anterior chamber at the angle. The tumor cells were slightly differentiated, with suggestion of acinar formation and mitotic figures. Neoplastic emboli were found in the vessels of the retrobulbar tissue and the extraocular muscles of both eyes.

DISCUSSION

DR. PERCE DELONG: Metastatic carcinoma is the commonest secondary tumor affecting the inner eye; nevertheless, its occurrence is rare.

Metastases are usually blood-borne, and, because of the number (about 20) of the short ciliary arteries these vessels are the most frequent route through which the emboli enter the inner eye. The site of the growth is also of importance because of the distribution of these vessels; the metastatic expression is usually on the temporal side and in the region of the macula.

Metastatic lesions of the anterior segment are rare, but 17 microscopically proved cases have been reported. In these cases the emboli were carried by one of the two long ciliary arteries. Involvement of the iris is extremely rare and usually occurs as an extension from the limbus. Bilateral metastatic carcinoma of the choroid has been recorded in the literature only four times. Metastatic extensions to the orbit are also rare; Reese, in his textbook "Tumors of the Eye," reports only 19 proved cases.

The globes in a case of bilateral metastatic carcinoma of the inner eye were presented. In each globe were three separate lesions, each the result of an implanted embolus. Two lesions in the right eye were the result of an embolus entering through a short ciliary artery; the third lesion, at the base of the iris and the ciliary body, was the result of an embolus entering through a long ciliary artery. It is regrettable that a gonioscopic examination was not made to determine whether this neoplasm could have been observed. In the left globe all three lesions must have been the result of emboli entering through the short ciliary arteries.

Metastatic carcinoma of the eye is a more frequent pathological entity than statistics would have us believe. These metastatic expressions appear in the late stages of the disease. The patient usually is not ambulatory, is debilitated, and seldom is cognizant of his visual impairment.

Furthermore, if the ophthalmologist will avail himself of the opportunity to visit a cancer ward, he will usually find several solid retinal detachments, which in all probability are metastatic lesions.

Reevaluation of Beta Radiation Therapy in Ophthalmology: Preliminary Results with the Sr^{90} Applicator. DR. WILLIAM F. HUGHES JR., Chicago:

In the past relatively few clinics have had radon available as a source of beta particles for the treatment of certain superficial conditions of the eye. Now that radium D-E and Sr^{90} applicators are commercially available to a larger number of physicians, it becomes more important that the ophthalmologist be aware of the rationale, indications, contraindications, doses, and dangers of beta therapy. I shall attempt (1) to reevaluate the results my colleagues and I have had in over 235 eyes during the past four years at the University of Illinois, using a radon application previously described (*Tr. Am. Ophth. Soc.* **50**:469, 1952), especially

in regard to the selection of cases and undesirable reactions, and (2) to present the preliminary results and certain disturbing problems of the new Sr^{90} applicator manufactured by Tracerlab, this portion of the work having been done by Dr. Fred M. Wilson, Indianapolis, and Dr. James E. McDonald, Chicago. For any new applicator it is necessary to know the physical characteristics, quality, and quantity of output.

The general doses of contact therapy used with the radon applicator are as follows:

Dose, Gm.-Sec.	
1	Inflammatory conditions
2-3	Initial doses; very sensitive lesions; lesions in children
4-5	Deep corneal vascularization; limbal tumors; vernal conjunctivitis

Comparison of the effect on the rabbit cornea of our radon applicator and a Sr^{90} applicator which was recently restandardized by Tracerlab, with use of a vanishing ion chamber, shows the output of our radon applicator roughly to be 2,000 rep per gram-second, (± 50%). Treatments are given every three to eight weeks, longer spacing and smaller doses in general being used now.

The general indications for beta therapy are the same as those for use of other types of radiation, such as x-rays or gamma radiation. The tissue to be destroyed must be more sensitive to radiation than the surrounding normal tissue. With extremely low doses, inflammatory conditions are apparently benefited. An indication for beta irradiation implies that this therapy not only is effective but is superior to other methods of treatment because of the still somewhat uncertain effects of radiation therapy on the eye.

Indications for Beta Radiation

Treatment of Choice	Epithelial tumors of limbus and cornea Vernal conjunctivitis, palpebral or bulbar forms, associated with severe symptoms Vascularization complicating keratectomy and keratoplasty Rosacea keratitis Primary vascularizing keratitis Recurrent pterygium (after secondary excision)
Favorable results (low doses)	Allergic and phlyctenular keratitis Papillomas and hemangiomas of conjunctiva Nodular episcleritis Granulation tissue
Uncertain results	Stromal herpes simplex (low doses) Basal-cell carcinoma of lid margin Chemical burns (not recent) Tuberculous sclerokeratitis Interstitial keratitis Trachoma, Stage IV Salzmann's dystrophy of cornea with vascularization Lipidal dystrophy of cornea with vascularization Old vascularized corneal scars
Not indicated because of undesirable features, better treatment available, or no effect	Primary treatment of pterygium Corneal scars without vascularization Fuchs's endothelial-epithelial dystrophy Epithelial downgrowth into anterior chamber Acute chemical burns Large doses for inflammatory lesions Cicatrizing conjunctival disease (e. g., pemphigus) Nevi Pinguecula Tumors of lid margin

Several complications have attended beta radiation therapy in some of these cases: 1. Irritability of the eye, lasting more than two weeks but eventually clearing entirely (10% of cases), following a dosage rate of 1 gm.-sec. or more per week, with a minimum total dose of 15 gm.-sec. applied anywhere on the surface of the globe. 2. Postirradiational vessels and telangiectases, which may develop one to three years after treatment with doses as low as 5 gm.-sec. in one area. 3. Epilation of the lashes, which may be produced by a dose of 4 to 6 gm.-sec. 4. Deep corneal ulceration which may follow ulceration or infection and direct application of excessively large doses directly over the area. This did not occur in our series. 5. Epidermization of the conjunctiva only when beta rays were used for epilation, the epidermis of the skin apparently overgrowing the conjunctival surface in the treated

area. 6. Glaucoma, which might be expected to be a complication of beta radiation therapy, rendering the limbal region ischemic. However, the diagnosis of glaucoma is difficult in cases of advanced keratitis because tonometric readings are unsatisfactory and associated conditions, such as iritis, can produce a secondary glaucoma independent of the beta radiation therapy. Glaucoma was suspected in seven eyes in which the total dose over the entire limbal region averaged 53 gm.-sec. 7. The possibility of cataract formation following large doses of beta radiation has not been reported until recently. In two eyes with severe primary vascularizing keratitis, 44 to 51 gm.-sec. in 16 to 18 weeks over the cornea and limbus resulted in cataract formation two and one-half to three years later. Two of these cataracts became rapidly intumescent and were extracted uneventfully except for somewhat retarded healing of the corneal incision, resulting in a filtering bleb. The other eye in one of these patients received 39 gm.-sec. within 34 weeks, and a posterior subcapsular cataract developed after approximately four years. This has not progressed during the past six months, vision remaining about 20/70. Two eyes with recurrent pterygium were treated with total doses of 28 gm.-sec. over a period of months and were found, upon wide dilation of the pupil two to three years later, to have small sector-shaped areas of vacuolation in the region of the equator of the lens beneath the area of treatment. These opacities are not detectable clinically through the undilated pupil. Owing to the uncertainty of the rep output of the applicator and some variability in the reported depth doses (viz., 2 to 11% at 3 mm., 1 to 7% at 4 mm., and 0.8% at 5 mm.), the amount of beta and gamma radiation reaching the lens (the average distance of the anterior capsule of the lens being about 3.5 mm. from the surface of the limbus and 4 mm. from the surface of the cornea) can be estimated only roughly. In the above cases of primary vascularizing keratitis in which cataracts developed perhaps 800 to 3,200 rep reached the lens. In the two cases of recurrent pteyrgium in which radon was applied only in one area directly over the limbus, and therefore only 3.5 mm. from the equator of the lens, where the "lens bow" of epithelium is located, perhaps 560 to 2,240 rep reached the lens.

The new radioactive Sr^{90}-Y^{90}-beta radiation applicator, first reported by Friedell, Thomas, and Krohmer in 1950, and studied by Wilson and McDonald, has several virtues, viz., long half-life of 20 years, relatively low cost, high output (40 to 100 rep per second) of pure beta particles of maximal energy 2.16 mev (slightly less than radon) and average energy of 0.8 mev (slightly more than radon), with depth doses comparable to those of radon. Its disadvantages include large size, with an active surface 7.8 mm. in diameter, uncertainty of evenness of layering of the Sr^{90}, and apparent technical difficulties in measuring the rep output by means of the vanishing ion chamber. Three applicators which have been restandardized after one or two years have shown an apparent drop of 33% in rep output. Until the physical method of measuring the surface output of these applicators becomes consistent, it is mandatory that each applicator be standardized on a rabbit cornea. Wilson has termed the dose necessary to produce a definite nebular opacity on the rabbit cornea that persists two to three months the "minimal inflammatory dose," or MID. With the change in physical measurements of the rep output, the minimal inflammatory dose has decreased from 36,000 to 20,000 rep. The clinical dose necessary to eliminate superficial corneal vascularization in humans is approximately 8,000 rep. (0.4 MID) according to the latest standardizations, and the skin erythema dose is about 1,400 rep (Wilson). The clinical results with the Sr^{90} applicator, using these doses, are comparable to those obtained with radon. In flat preparations of rabbit lenses, Wilson has found nuclear pyknosis, fragmentation, and balloon cells in some of the epithelial cells 100 days after exposure to 1.7 minimal inflammatory dose (34,000 rep). No clinical signs of cataract were present; and this does not represent a threshold dose.

What is a safe, noncataractogenic dose of beta radiation? Unfortunately, such data are not available even for x-ray and gamma emanations, whose ionization can be measured accurately. Cataracts can be produced in rabbits with x-ray doses as low as 200 r, but have not been reported in humans with divided doses totaling

400 r, and can, but not necessarily, be produced by 1,000 r. Assuming that 400 r is noncataractogenic and that x-rays can be approximately equilibrated with beta rays, a depth dose of 5% at 4 mm. using beta radiation would indicate a noncataractogenic dose of only 8,000 rep of beta radiation applied to the surface of the cornea. It is probable that this dose is unduly low for the following reasons: 1. The reported rep output of the beta applicators may still be unduly high on an absolute basis which could be compared with the ionization produced by x-rays. 2. The entire lens is not exposed after treatment with small beta applicators, so that the safe dose may be 8,000 rep in any one area. 3. The possibilities exist that histological changes in the lens epithelium can take place without cataract formation, that recoverability is possible, or that opacities may remain localized and nonprogressive.

In conclusion, the question probably arises: Is beta radiation too dangerous to use on the eye? Beta radiation, especially with the new Sr^{90} applicator, should still be considered experimental. A more consistent physical measurement of output is needed, so that clinical doses can be standardized and more accurate depth doses be obtained. Beta radiation should be used only in specific cases in which it has a good rationale and is superior to all other methods of treatment. Minimal doses and more prolonged intervals between treatments should be employed. A calculated risk of cataract is present if a total dose of over 10 gm.-sec. of beta radiation is given in any one quadrant and more than 30 gm.-sec. over the entire globe with a radon applicator of our size, and an estimated 16,000 rep in one area with the Sr^{90} applicator.

George F. J. Kelly, M.D., *Chairman*

M. Luther Kauffman, M.D., *Clerk*

April 16 1953

Acute Hypotony. DR. P. ROBB MCDONALD.

An Elliot trephination had been performed on the right eye for acute glaucoma in 1943. The eye had been hypotensive thereafter, but the patient had 6/9+ vision until September, 1951, when she was struck in the right eye with an elbow. The vision failed rapidly. There was no evidence of a ruptured cystoid scar; the anterior chamber was formed. Ophthalmoscopic examination revealed papilledema and elevation of the macular region of 2 to 3 D. Vision was limited to perception of hand movements, and the tension was too low to be recorded.

Operation consisted of resection of the cystoid scar and closure of the trephine bleb. Recovery of vision was fairly prompt. There was a return of the patient's glaucoma, but this has been controlled by miotics. Gonioscopic examination revealed a narrow, but open, angle. Examination of the left eye showed an essentially normal condition. The visual fields did not reveal any changes suggestive of glaucoma.

DISCUSSION

DR. EDMUND B. SPAETH: This case is a remarkable counterpart of the one I presented before this Section about 10 years ago, though the result in that case was not as fortunate as was this in Dr. McDonald's. My patient, the mother of a physician, had had a Lagrange sclerotomy. About eight months later there developed a hypotony so profound that the weight of the lid, with the pull of the superior rectus muscle, caused a deformity of the cornea and of the globe. The sclerectomy incision was closed in a way somewhat similar to the method used by Dr. McDonald. Very shortly after that there developed a marked return of chronic inflammatory hypertension. An iris inclusion operation was done. The reestablished glaucoma was controlled for a short time, but the eye was ultimately lost as a result of the chronic inflammatory secondary glaucoma.

I have not the slightest idea of what is the correct therapy for acute hypotony! Severe hypotony has been reported to follow corneoscleral trephining. It has been seen after cyclodialysis and after cycloidiathermy. Personally, I know of no case in which it has developed after an iris inclusion. It is quite logical to wonder whether this hypotony could be a manifestation of inflammation rather than a result of excessive filtration. If it is the former, certainly, further surgical intervention is contraindicated. If it is the latter, one runs a strong chance of reestablishment of the original glaucoma, with more tissue trauma from further surgery for the hypotony. The effect which these extreme fluctuations in intraocular tension have upon the intraocular capillary bed must be serious.

In Dr. McDonald's case there has been a most fortunate outcome. I am curious to know what the result will be in another year. Postoperative hypotony continues to be inexplicable as to cause, controversial as to effect, and unanswerable as to treatment.

Follow-Up Study of 39 Patients with Glaucoma Treated with Cyclodiathermy.

(By invitation) DR. BERNARD E. LACHMAN and DR. PAUL A. ROCKWELL.

The authors reported the results of perforating cyclodiathermy in 39 glaucomatous eyes treated by the method recommended by Castroviejo. All patients were under observation from one to two years. Of these 39 patients, 17 had cyclodiathermy as a primary procedure, while in the remaining 22 the operation followed other glaucoma surgery, which had failed.

The result was considered successful when (1) the tension was consistently below 30 mm. Hg (Schiøtz) during the period of observation; (2) when there was no loss of visual field, and (3) in the case of a blind eye, when there was relief from pain but no atrophy of the globe. In only seven cases was treatment considered successful by these criteria. No conclusion could be drawn as to the merit of the procedure in any type of glaucoma. All patients required miotics after operation and had a rise in tension when use of miotics was discontinued. Twelve patients with chronic simple glaucoma were treated, 8 with poor and 4 with good results. For seven aphakic patients with glaucoma the operation was a failure. In two of these atrophia bulbi subsequently developed. All the nine patients with absolute glaucoma in this series represented therapeutic failures. In three of these hypotony and subsequent atrophy of the globe developed. Of five patients with congenital glaucoma, all of whom had had previous glaucoma surgery with failure, cyclodiathermy was successful in two and failed in three. Five patients had their glaucoma controlled for periods varying from 4 to 11 months and then had a rise in tension despite use of miotics. Two patients suffered a loss in visual acuity shortly after the operation procedure. In one patient with acute glaucoma atrophy of the globe developed 11 months after operation. Six patients showed a postoperative rise in tension above preoperative levels, this increased tension persisting despite medical therapy. Of the 39 patients, 6 had atrophy of the globe.

The authors concluded that the results of perforating cyclodiathermy by the method which they employed are unpredictable. The procedure is simple but not entirely safe. It may be followed by loss of visual acuity, a persistent rise in tension, or atrophy of the globe.

DISCUSSION

DR. HAROLD G. SCHEIE: Cyclodiathermy should be evaluated from two points of view: (1) the results obtained by the original technique, that is, the one advocated by Vogt, and (2) the effectiveness of the newer methods of the past two or three years. Vogt originally suggested that the electrode should be placed up to within 2.5 to 3 mm. of the limbus. The present-day techniques, as suggested by Castroviejo, in this country, and Weekers and Reiser, in Europe, all recommend applying the current 6 mm. or more from the limbus. In our experience at

the Hospital of the University of Pennsylvania, the older method is dangerous because corneal opacity frequently results from damage by the current. The newer technique has proved to be quite safe.

From approximately 1947 until the middle of 1949, we used cyclodiathermy on a total of 17 eyes. The operation failed to control the tension in 10 eyes, and corneal opacity due to edema occurred in 6. We therefore discontinued use of the procedure until January, 1951. We then adopted the newer technique and used it on 29 eyes. All these eyes have been kept under observation for from one to two years. The electrode was applied no closer than 6 mm. from the limbus, 9 to 12 applications being made. The tension was controlled in 14 eyes, but in 4 miotics were required. In several of the patients reoperation was necessary because of a late recurrence of elevated tension. We do not believe the operation is the ideal approach to the treatment of glaucoma, largely because of this tendency of the increased tension to recur. There were, however, no serious complications, as with the original technique. Severe iridocyclitis occurred in one patient, with recovery. We have had none of the serious complications mentioned by the authors. However, we still reserve the procedure for use when other operations have failed or may be contraindicated.

Retinopathy of Prematurity (Retrolental Fibroplasia) and Its Relationship to Oxygen. Dr. Robert Bedrossian (by invitation).

The term "retinopathy of prematurity," as suggested by Heath, should be used instead of retrolental fibroplasia, since it limits the disease to that condition found in the premature infant and since in most cases of retinopathy a retrolental membrane does not develop.

The classification of the stages of the disease according to Bousquet was thought to follow the clinical course most closely.

The recent literature, claiming a relationship between the routine administration of oxygen and the development of the disease, was briefly discussed.

An analysis of 44 cases of retinopathy occurring among 127 premature infants weighing under 4 lb. (1,814 gm.) at birth showed that in the great majority the disease developed shortly after the oxygen supplement was completely withdrawn. Thirteen infants with rapidly progressive retinopathy showed rapid improvement within two weeks when they were given oxygen therapy. Eleven of the 13 infants had a recurrence of the disease when the oxygen therapy was stopped. Statistical analysis showed that the group with retinopathy had oxygen for a longer time, but had a more rapid weaning from oxygen, than the group without retinopathy. Retinopathy of prematurity appeared in two infants during the course of pneumonia and subsided when the pneumonia resolved.

The authors drew the following conclusions:

1. Oxygen is not the direct cause of the disease, but use of high oxygen concentrations over a long period may predispose to the disease.

2. The commonest precipitating factor in the disease is probably the too rapid lowering of the oxygen concentration of the infant's environment.

3. Retinopathy of prematurity may also be precipitated by pneumonia and other respiratory infections.

4. The active vascular phase of the disease may be arrested by placing the infant so affected in the same oxygen environment from which he was withdrawn prior to the development of the disease.

DISCUSSION

Dr. William O. LaMotte Jr.: Dr. Bedrossian's fine presentation serves admirably to dispel the doubts of those who still are skeptical concerning the relation of oxygen to the retinopathy of prematurity. It also points up dramatically

the necessity for ophthalmoscopically guided oxygen control of premature infants. I can only corroborate from my own experience the dramtic reduction in incidence of this blinding disease since the adoption of such measures of oxygen control. Specifically, as previously reported, the incidence of this disease in bilateral blinding form at the Delaware Hospital, in Wilmington, during the four-year period from 1948 through 1951 was 33.8% in all infants weighing 4 lb. or under at birth. This incidence did not vary with the form of therapy, including administration of vitamin E and corticotropin, the incidence in 1951, for example, being 38.8%. Beginning in Jan. 1, 1952, my colleagues and I adopted the suggestions and methods of Szewcyck, with a striking reduction, to 3.7%, in the incidence of the disease during 1952. This figure was based on 27 infants under 4 lb. at birth, 18 of whom showed various grades of the retinopathy of prematurity. This proportion is consistent with the expectation that two-thirds of all infants of this birth-weight group will show some signs of the disease. Normally, it would be expected that one-half of these would return to normal spontaneously and one-half would show progression to permanent changes. Actually, only four of the total number show any permanent changes at all, and three of these will have normal vision in at least one eye. Only one of the whole group has bilateral retinal detachments, giving us the incidence of 3.7%. One cannot but be impressed by the fact that the incidence of this disease in blinding form has dropped from 1 : 3 to 1 : 27 since the adoption of methods for oxygen control.

I agree with Dr. Bedrossian's conception of a secondary anoxia being the chief mechanism involved in this disease. I would take exception, however, to his implication that the eyes which will show the retinopathy are usually normal while the infant is still receiving oxygen. Most of the eyes are abnormal, because the retinal arterioles, although not engorged and tortuous, are usually very narrow. As I reported to this group in December, 1949, extreme narrowing and attenuation of the retinal arterioles constitute one of the first signs of this disease. Although almost all infants who have been in high oxygen concentrations for any length of time will show narrowing of the arterioles, those showing the most extreme attenuation may assuredly be suspected of being those in whom the retinopathy of prematurity is most likely to develop after removal from oxygen. This narrowing is, therefore, an advance notice of those infants who are probably the most unstable and most sensitive to metabolic changes. If anyone should doubt the relationship of oxygen to the caliber of the retinal vessels, let him take, for example, an infant weighing 5½ lb. (2,500 gm.) at birth, in whom the chances of precipitating a permanent change are remote, and keep the child in a 90% oxygen concentration for several days, and then suddenly remove him to room air. The observer will see, within the course of one to two days, an increase in the caliber of the retinal vessels to two or three times the normal; these vessels, on reintroduction into high oxygen concentration, will return to normal in another two or three days, a process requiring a week to 10 days without the reintroduction into oxygen.

I should like to conclude with the following axioms, applicable to this situation. Premature infants in the weight group predisposed to the development of this disease should receive oxygen in the lowest concentration for the shorest period of time compatible with their survival. Except in the most unusual circumstances, the oxygen concentration should never be above 50%. Oxygen concentration should be determined by actual measurements of the oxygen concentration, and not by liter flow. For example, the same liter flow per minute in two different Isolettes has been found to vary as much as 30%. The value of an Isolette is not in the high concentrations of oxygen which can be developed but in the fact that stable and steady oxygen concentrations can be maintained without wide fluctuations, which tend to activate the instability of the immature vascular systems. Careful ophthalmoscopic control has become a necessity in the management and conduct of a premature infant nursery.

Chronic Progressive External Ophthalmoplegia: A Clinical and Neuropathologic Report. (by invitation) Dr. Gabriel A. Schwarz and Dr. Chan-Nao-Liu.

There is a disease of man characterized by weakness of the muscles of the eyelids and weakness of the external muscles of the eyeballs. This disease is slowly progressive over many years. It shows an occasional familial incidence. Some authors have expressed the belief that the condition was the result of disease of the neurones in the brain stem which supply these muscles; others more recently have emphasized the resemblance of this condition to muscular dystrophy.

Our patient, a white man, died at the age of 63, of a spongioblastoma polare of the left parietal lobe. At the age of 27 he had begun to have drooping of the left upper eyelid; at 41 ptosis had begun on the right side. The onset of weakness of the movements of his eyeballs was so insidious that no definite time of onset could be established. Examination a year before his death showed bilateral ptosis, the eyeballs in primary position, and only barely perceptible movements of his eyeballs, either voluntary or reflexly. The pupils were equal, regular, and round and reacted well to light but poorly in attempted convergence. Otherwise, the cranial nerves were intact.

Neuropathologic studies of the oculomotor, trochlear, and abducens nuclei showed (1) the cellular populations to be unchanged, (2) the motor neurones to be somewhat smaller, less polygonal, and rounder than usual, (3) cytoplasmic clumps of granular yellow-brown pigment, and (4) vacuoles in the perikaryon of some cells. In the abducens nucleus, chromatolysis was also noted, but there were many more intact neurones. One of the masticator nuclei contained neurones with definite chromatolysis.

The intra-axial portions of the oculomotor, trochlear, and abducens nerves were readily identified in myelin preparations and showed no demyelination. The extra-axial portions of these nerves also showed no demyelination. The oculomotor nerves seemed to have a general overabundance of nuclei throughout. A count of the axis-cylinders of the right trochlear nerve showed no significant difference from the fiber count in a normal control.

The left superior oblique, the left superior rectus, and the right lateral rectus muscles were found to have undergone a marked and diffuse destruction and loss of muscle fibers. The remaining muscle fibers showed many and varied changes. Large and small fibers were seen. In some fibers myofibrils were swollen and torn apart. Portions of muscles were hyalinized. Areas of muscles were granular. A few fibers looked fairly normal. In one muscle fiber there were the following alterations: The sarcolemmal nuclei about the muscle fibers were greatly increased. Fat and connective tissue replacement and overgrowth occupied much of the muscles. Stains for myelin and for axis-cylinders disclosed abundant intact intramuscular nerve fibers. Motor end-plates could be identified on severely degenerated muscle fibers or apparently free in the loose connective tissue. Elaborate spiral nerve endings were also found about degenerating muscle fibers.

Studies of both ciliary ganglia revealed finely myelinated nerve fibers. The ganglion cells showed the usual histologic variations seen in these autonomic neurones, but no pronounced or consistent pathologic change.

The establishment of any particular wasting muscular disease as being "primary" or "secondary" is not always simple. More recent studies have emphasized the need to observe the intramuscular nerve fibers and nerve endings. Such studies had never been done before in this disease. In our case, the changes in the extraocular muscles were typical of changes described late in muscular dystrophy, but the significant finding was the preservation of abundant nerve fibers and the presence of motor nerve endings in association with an intense destruction of muscle fibers. These findings, coupled with the preservation of the intra-axial and extra-axial nerve fibers supplying the diseased muscles and the relatively healthy motor nerve cell bodies of the nuclei which gave rise to the motor nerves to the abnormal

muscles, seem to us to favor the opinion expressed by Kiloh and Nevin (1951) that chronic progressive external ophthalmoplegia is a form of muscular dystrophy and could rightfully be called "ocular myopathy."

DISCUSSION

DR. FRANCIS HEED ADLER: The question at issue is whether the pathogenesis of chronic progressive ophthalmoplegia is primarily in the nuclei of origin of the ocular muscles or in the muscles. Wilbrand and Saenger, who first collected a series of cases of this disorder, suggested that the disease was primarily due to a degeneration of the cells in the nuclei of the third, fourth, and sixth nerves. This was borne out by the pathological report of a case by Langdon and Cadwalader. These authors found a diminution in the number of cells in the nucleus of the sixth nerve but were uncertain about the counts in the third nucleus. They did not examine the extraocular muscles.

It is obvious that in order to decide this question one must examine the nuclei of origin of the nerves, the nerves, and the muscles. Dr. Schwarz has done this and has found no changes in the nuclei. The nerve fibers were not reduced in number. However, he did find changes characteristic of myotonic dystrophy in the muscles. One must assume that the cases of so-called chronic progressive ophthalmoplegia belong in the group of ocular myopathies and are due to some primary disturbance in the ocular muscles.

Obituary

EDWARD VAIL LAPHAM BROWN, M.D.
1876-1953

Dr. Edward Vail Lapham Brown died on March 1, 1953, at his home in Winnetka, Ill.

His place not only as an ophthalmologist but as an outstanding teacher and public-spirited citizen will be difficult to fill.

Ophthalmology, both in Chicago and in the world, has suffered a severe loss. He will be remembered not only as a scientist but as a devoted family man. In August, 1912, he married Frieda Muench Kirchoff, and their family consists of four boys and one girl.

In Vienna, in 1911, "E. V. L.," as his close friends called him, became engaged to Miss Kirchoff, who was teaching English and revising Professor Meller's medical lectures in English.

Dr. Brown's career was a full and rewarding one. He was born in Morrison, Ill., on Aug. 15, 1876. He first attended Hahnemann Medical College, graduating in 1896. Later he attended Rush Medical College, graduating in 1898. He interned at the Illinois Charitable Eye and Ear Infirmary in 1899 and was made assistant to Dr. F. C. Hotz.

It was at this time that he entered the University of Chicago, taking his degree in 1902. He then took up graduate work in ophthalmology in Berlin in 1902, and later in Vienna, under Fuchs and Meller, in 1907. His Vienna visits occurred in 1911, 1912, 1925, 1926, and 1929.

His work was recognized by many organizations in this country. In 1940 he was made president of the American Ophthalmological Society. He received the Howe medal in 1945 and the Leslie Dana medal in 1951 for his interest in the prevention of blindness.

Among his appointments were those of attending oculist, Presbyterian Hospital and Cook County Hospital; assistant professor of eye pathology, University of Chicago; assistant professor of ophthalmology, Rush Medical College, and professor of ophthalmology and head of the department, University of Illinois College of Medicine, 1917 to 1926. He had been president of Provident Hospital for four years at the time of his death. He was president and founder of the Hadley School for the Blind.

Dr. Brown was a member of the American Medical Association, the Illinois State Medical Society, the American Ophthalmological Society, the Chicago Ophthalmological Society (ex-president), and the Institute of Medicine. He was a member of University Club, Quadrangle Club, Indian Hill Golf Club, and Arts Club.

In his teaching, Dr. Brown instituted such new methods as emphasis on out-patient-department teaching; regular attendance of chief and assistants at clinics; the staff-resident system at the County Hospital, University of Illinois, Billings

EDWARD VAIL LAPHAM BROWN, M.D.
1876-1953

Hospital, and Presbyterian Hospital; volunteer-assistant training preliminary to assistant residency, and lay-clinical-technician training.

Dr. Brown's published papers were numerous. He translated von Salzmann's "The Human Eyeball" and Fuchs's "Diseases of the Human Eye," and he was active to the last.

FRANK BRAWLEY, M.D.

News and Comment

GENERAL NEWS

Brooklyn Eye and Ear Hospital.—A course on glaucoma, with particular emphasis on gonioscopy and study of the angle of the anterior chamber, will be given at the Brooklyn Eye and Ear Hospital on Nov. 16, 17, and 18, 1953. Ample opportunity for practical instruction in the use of the goniolens will be given, and material from the glaucoma clinic will be utilized. One afternoon will be devoted to surgical indication and technique of glaucoma surgery in the operating room.

This course will be given by Dr. Daniel Kravitz and the staff.

Application and the fee of $40 for registration of ophthalmologists may be addressed to Dr. Daniel Kravitz, Brooklyn Eye and Ear Hospital, 29 Greene Ave., Brooklyn 38.

SOCIETY NEWS

American Ophthalmological Society.—At its recent meeting the American Ophthalmological Society elected the following officers for the coming year: president, Dr. William L. Benedict, Rochester, Minn.; vice-president, Dr. Everett L. Goar, Houston, Texas; secretary-treasurer, Dr. Maynard C. Wheeler, New York, and editor, Dr. Gordon M. Bruce, New York.

PERSONAL NEWS

Appointment of Dr. Bernard Becker.—Dr. Bernard Becker, at present at the Wilmer Ophthalmological Institute, has been appointed Professor and Head of the Department of Ophthalmology, Washington University, replacing Dr. Lawrence T. Post, who retired from these duties July 1, 1953. Since Dr. Becker will be unable to assume his duties until about Jan. 1, 1954, Dr. T. E. Sanders has been appointed temporary acting head of the department.

Books

Syphilitic Optic Atrophy. By Walter L. Bruetsch, M.D. Price, $5.50. Pp. 140, with 30 illustrations. Charles C Thomas, Publisher, Springfield, Ill., 1953.

This valuable monograph on syphilitic optic nerve atrophy was written by a neurologist who is a recognized authority on syphilis of the central nervous system.

The author points out that over 30,000 persons are blind in the United States as the result of syphilitic optic nerve atrophy. He summarizes and refutes four new theories of the pathogenesis of primary syphilitic optic nerve atrophy, namely, disturbance of the sympathetic nerve control; the theory of the interrelationship of systemic blood pressure, retinal blood pressure, and intraocular pressure; the theory which assumes that optic nerve atrophy follows optochiasmatic arachnoiditis in every case, and, finally, the vitamin-deficiency theory. Regarding the last, he states that, although degeneration in the spinal cord, and sometimes in the optic nerve, may occur as a direct result of diets deficient in vitamin A, vitamin B, or both, there is no evidence which justifies the introduction of nutritional deficiency as a factor in the causation of syphilitic optic nerve atrophy. The pathogenesis of this condition, he believes, can be explained as an effect of syphilis alone, localizing to an intense degree in the optic nerves and chiasm. If, in addition to an infectious agent, one needs another factor for the production of syphilitic optic nerve atrophy, the author prefers to assume an inherent susceptibility of the nerve fibers to degeneration. Bruetsch believes that syphilitic optic nerve atrophy is always an inflammatory process, mainly situated in the intracranial portion of the optic nerves and in the chiasm, followed by a secondary degeneration of the nerve fibers.

In this monograph the author reports on the histologic examination of the optic pathways in 80 cases. Fifty-seven of these were cases of dementia paralytica or tabetic dementia paralytica. Twenty cases were of meningovascular syphilis and 3 of tabes dorsalis. For comparative reasons, optic nerve atrophies caused by conditions such as brain tumor or multiple sclerosis were studied microscopically at the same time. He points out that although syphilitic optic nerve atrophy is often referred to as tabetic optic nerve atrophy, the principal similarity between tabes dorsalis and so-called tabetic optic nerve atrophy is the chronic syphilitic inflammation. The inflammatory phase of syphilitic optic nerve atrophy is generally more in evidence than the inflammatory component in the posterior roots and in the spinal meninges in cases of tabes dorsalis. Stress is laid on the degree of inflammation within the optic nerves and the length of time before optic nerve atrophy occurs.

Bruetsch considers that syphilitic optic nerve atrophy begins in the intracranial portion of the optic nerves, or in the chiasm, or in both, and the atrophy of the visual nerve fibers proceeds in both directions. The Treponema pallidum was not found in any of the author's cases, and he explains the reasons for the absence of spirochetes in the optic nerves in syphilitic optic nerve atrophy by the fact that the optic nerves represent white matter, and that it is admittedly difficult to locate spirochetes in the white matter of the brain in cases of dementia paralytica. He emphasizes that the visual fields are the most important diagnostic means in estimating the anatomic damage to the optic nerves and that an isolated field defect in a patient with syphilis should suggest beginning optic nerve atrophy. Four fundamental types of field defects are described: (1) concentric contraction of the peripheral field, associated with late loss of visual acuity; (2) sector-shaped visual field defects, with which loss of vision may be early or late; depending on involvement of the papillomacular bundle; (3) central or cecocentral scotoma with normal peripheral fields, associated with early loss of visual acuity, and (4) central or cecocentral scotoma with defects in the peripheral fields, also associated with early loss of vision.

The author advises the treatment of syphilitic optic nerve atrophy on the same basis as the therapeutic approach in cases of dementia paralytica. He believes that we have as yet not had sufficient experience to draw final conclusions regarding the effectiveness of antibiotic therapy, but suggests that the time has probably come when fever therapy may be abandoned, particularly fever induced by malaria, in favor of the use of penicillin alone. He points out that in this country the optometrist sees a third of the patients with early optic atrophy who later attend ophthalmological clinics, and he emphasizes that the average 18-month delay between onset of impaired vision and institution of proper treatment is another serious handicap to treatment and to the prevention of blindness from this disease.

Although small, this book is a gold mine of valuable information, and it is strongly recommended to all ophthalmologists.

Ocular Therapeutics. Second Edition. By William J. Harrison. Price, $6.50. Pp. 284. Charles C Thomas, Publisher, 301-237 E. Lawrence Ave., Springfield, Ill., 1953.

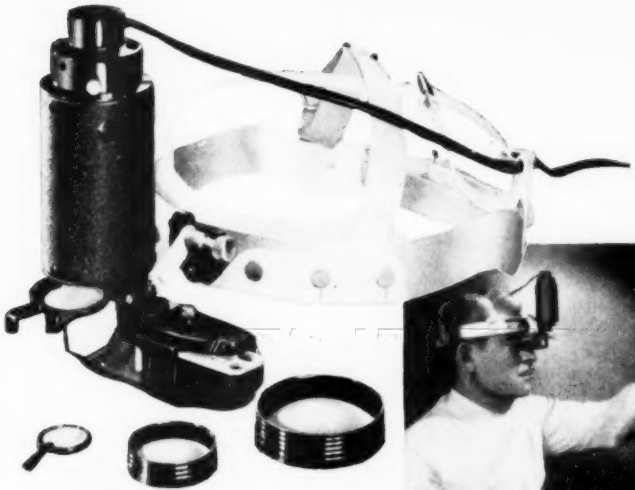
The new edition of this small book on ocular therapeutics contains two new chapters, on anticoagulants and cortisone and corticotropin. The format has been changed to provide a so-called handy pocket size. This is not to be taken too literally, but it is of advantage to have a relatively small book for handy desk use. The value of a book of this sort depends largely upon the arrangement of material and the index. The book is well indexed from the point of view of finding a desired drug the name of which is known. On the other hand, the index leaves much to be desired when it comes to checking the latest form of treatment of a particular disease. A better index would materially improve the volume, which contains much useful information.

The Human Senses. By Frank A. Geldard. Price, $5. Pp. 365, with 104 illustrations. John Wiley & Sons, Inc., 440 4th Ave., New York, 1953.

Although written by a psychologist, this book is an excellent text on sensory physiology. The book covers the physiology of the eye and the ear, the senses of smell and taste, and the modalities of pressure, pain, and temperature. There is also a chapter on labyrinthine sensitivity.

Of particular interest to ophthalmologists is, naturally, the section dealing with the physiology of the eye. This covers eighty pages and considers the visual stimulus, the photochemical changes in the retina, the electrical responses in the retina and optic nerve, and, finally, the various qualities of vision, such as basic visual phenomena of absolute and differential thresholds, adaptation, visual acuity, contrast and interaction, and color vision.

The material is clearly written and well documented with line drawings. It is a valuable addition to the growing number of books on the physiology of the eye.



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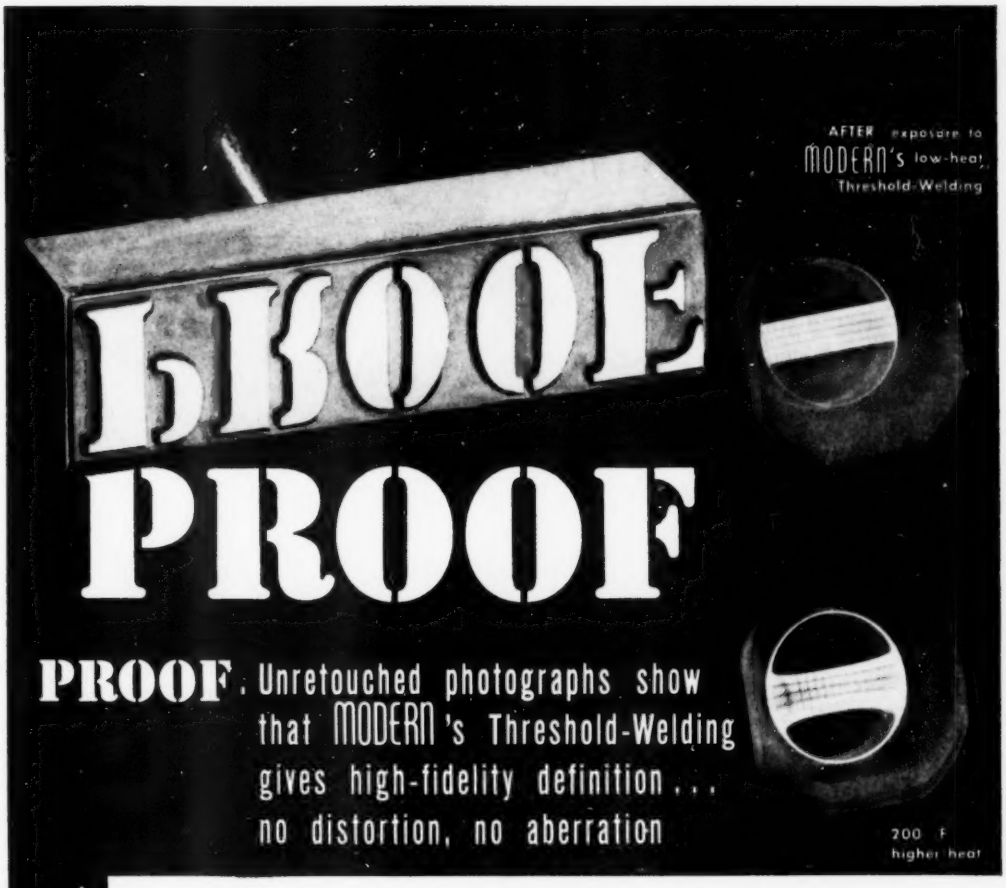

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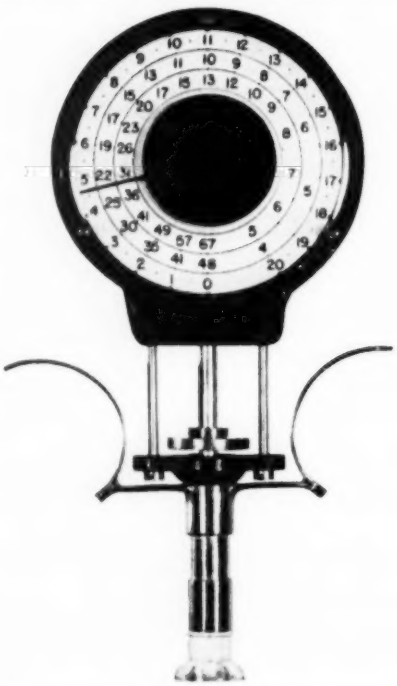

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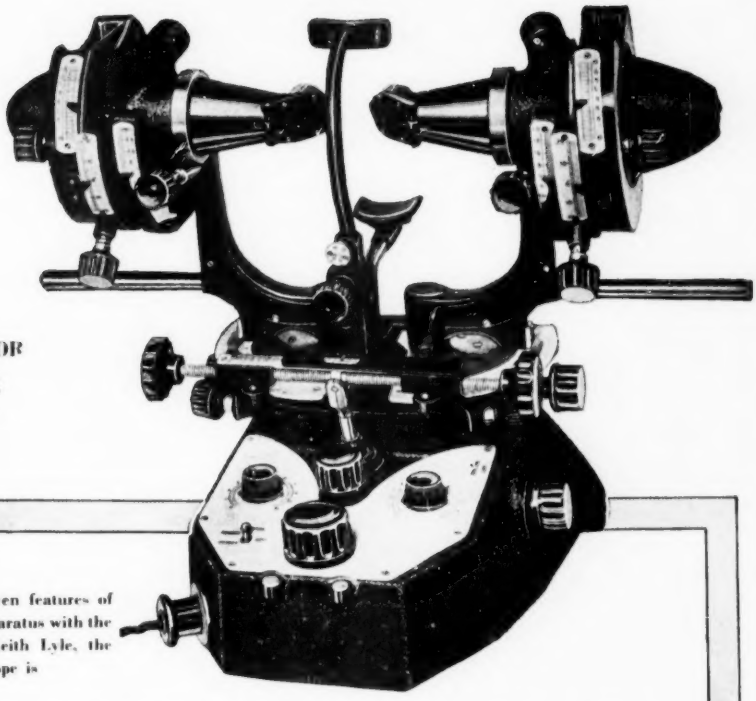

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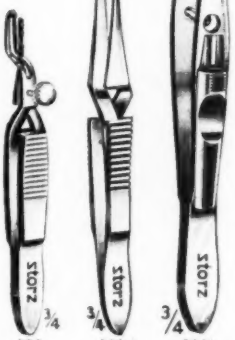

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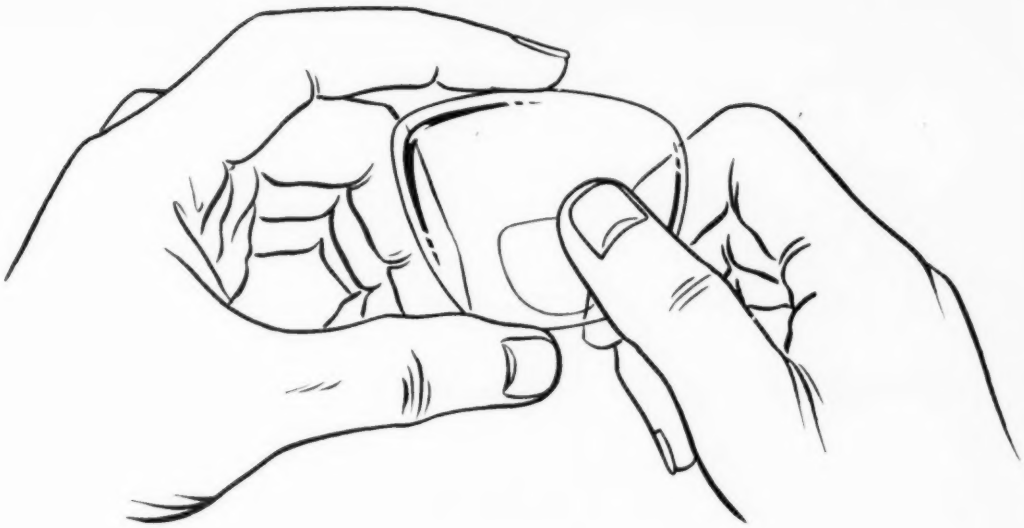

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Segment size: 24 x 17mm. A wider field at reading level with all other Panoptik advantages.

Soft-Lite Orthogon Panoptik (Prism Segment)

Segment size: 21.5 x 14.5mm. Segment size and shape are slightly different from regular Panoptik bifocals. Therefore, PR blanks should be used in both lenses of a pair.

Soft-Lite Orthogon Panoptik (Double Segment)

Lower segment same as regular Soft-Lite Panoptik; upper segment is round. On factory prescription.

Soft-Lite Panoptik Trifocal

Overall segment size: 24 x 17mm; intermediate field, 6.0mm high. Intermediate is 66% of reading addition.

Soft-Lite Panoptik Trifocal (Double Segment)

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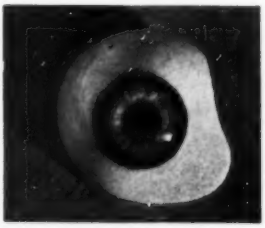

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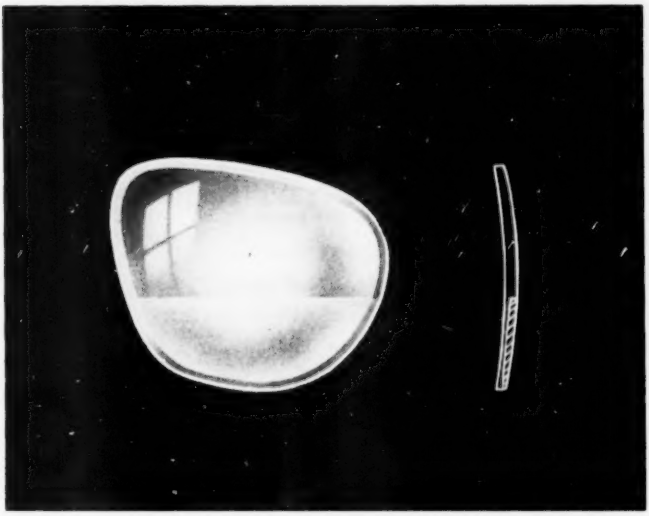

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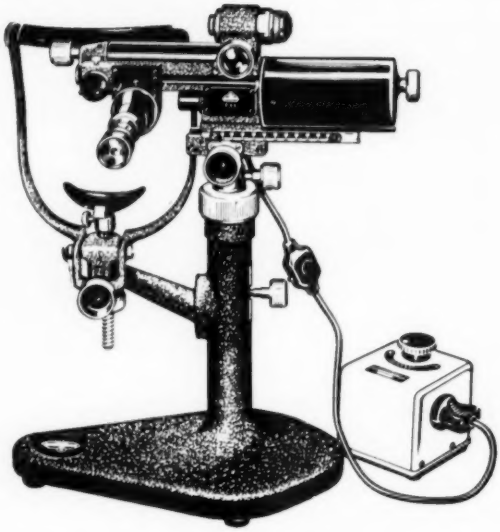

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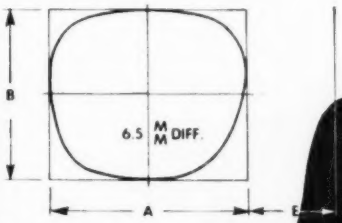

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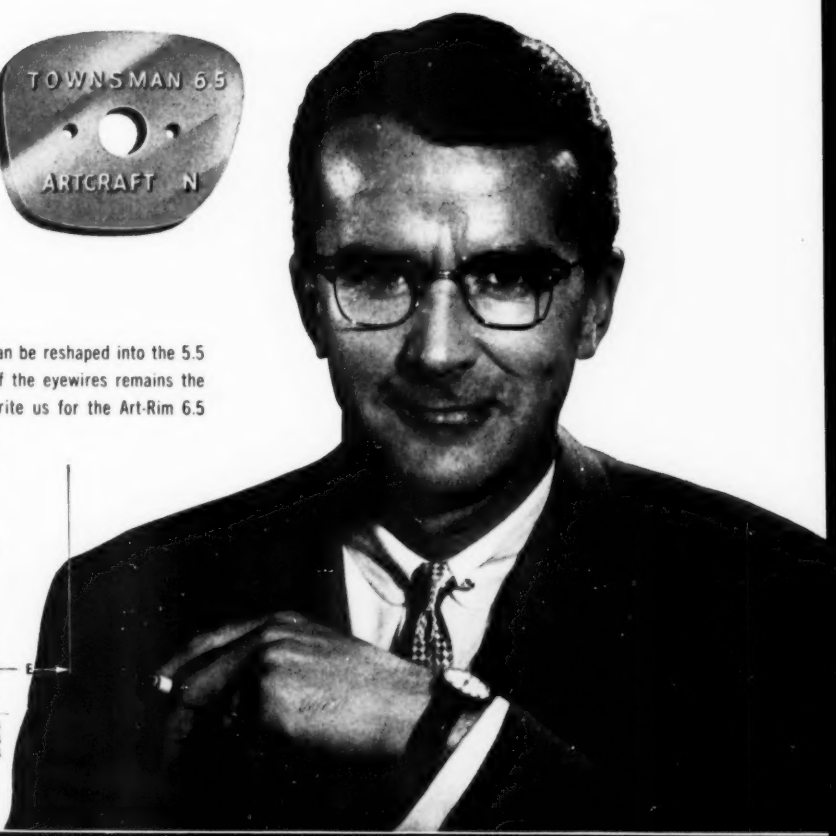

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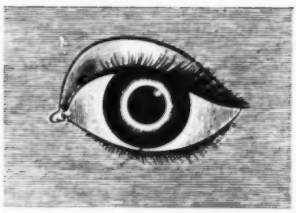

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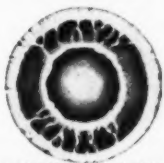

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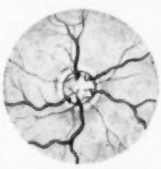

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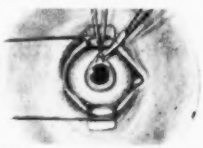

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